Cognitive Control in Schizophrenia

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Submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

in the Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY

2014

ABSTRACT

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Schizophrenia is the ninth leading cause of disability worldwide (e.g., Lopez et al., 2006), and is a devastating psychiatric illness. Although diagnosis is made based upon the occurrence of positive and negative symptoms (First, Spitzer, Gibbon & Williams, 1995), it is the cognitive symptoms that are most strongly associated with functional outcome (Green, 1996). Cognitive control, including the ability to appropriately update relevant information and resist interference from irrelevant information, is critical for flexible and adaptive goal-directed behavior, and is among the most frequently noted of the cognitive symptoms in schizoprenia (Barch, 2005; Barch & Smith, 2008). Despite this, deficits in cognitive control are unaffected by medications used to treat the clinical symptoms of the disorder (Greene et al, 2008). Understanding both the behavioral and the neural mechanisms that comprise this deficit is thus of paramount importance. Although deficits in cognitive control in schizoprenia have been extensively studied, a number of questions still remain. Here, I ask two main questions: First, is cognitive control impaired globally, or are only certain aspects of cognitive control impaired in schizophrenia? I found that that there are (at least) two different selection mechanisms, and that people with schizophrenia are impaired in only one of these: dysregulation in left posterior ventrolateral prefrontal cortex correlates with impaired behavioral performance on a working memory task, suggesting that deficits in inhibiting irrelevant information from working memory is the crux of the deficit. Second, I asked whether the nature of the information affects cognitive control. I found that

people with schizophrenia are able to deploy cognitive control processes more effectively than healthy controls in cases in which salient, emotional information competes with active cognitive goals, suggesting specific underlying deficits in emotional processing.

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Acronyms

BA	Broadmann Area
BOLD	Blood Oxygenation Level-Dependent
BPRS	Brief Psychiatric Rating Scale
DIGS	Diagnostic Instrument for Genetic Studies
DLPFC	Dorsolateral Prefrontal Cortex
FMRI	Functional Magnetic Resonance Imaging
HC	Healthy Controls
IPS	Intra-Parietal Sulcus
NYSPI	New York State Psychiatric Institute
PANSS	Positive and Negative Syndrome Scale
PSZ	People with Schizophrenia
ROI	Region-of-Interest
RT	Reaction Time
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SCID	Structured Clinical Interview for DSM-IV
SZ	Schizophrenia
VLPFC	Ventrolateral Prefrontal Cortex
WM	Working Memory

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Peer Reviewed Papers

Ahmari, S., Eich, T. S, Cebenoyan, D., Smith, E. E. & Simpson, B. H. (invited; under review). Assessing neurocognitive function in psychiatric disorders: a roadmap for enhancing consensus. *Neurobiology of Learning and Memory.*

Eich, T. S., Nee, D., Insel, K., Malapani, C & Smith, E. E. (2014). Neural correlates of impaired control over working memory in Schizophrenia. *Biological Psychiatry*.

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Acknowledgements

Thanks to Edward E. Smith, who I am fortunate enough to call my mentor and friend. I miss you terribly.

Thanks to my parents Janet Metcalfe and Eric Eich, for your boundless encouragement and generosity of spirit and mind.

Thanks to my husband James Billett, your patience, support, and willingness to always listen and give me advice.

Thanks to my sweet boys Jackson and Kai, for filling my life with joy and light.

Thanks to my dissertation committee, BJ Casey, Kevin Ochsner, Daphna Shohamy, Dean Mobbs and Jerry Bruder, for all of your support and feedback.

Thanks to all of the people who took time to participate in the studies, and to Ragy Girgis, Joshua Kantrowitz, Jacob Ballon, Roberto Gil, Winnie Leung and Nicole Gaine at NYSPI for their help recruiting and screening participants.

And thanks to the Columbia University Department of Psychology and the Graduate School of Arts and Sciences, for your generous funding.

For Ed

Introduction

Schizophrenia (SZ) is a severe brain disorder that affects how a person thinks, acts and feels. The term "schizophrenia" was first coined by the Swiss psychiatrist Eugen Bleuler in 1911 from the Greek roots *skhizein* (to split) and *phrenos* (mind). By a "splitting" of the "mind", Bleuler was referring to a loosening or fragmenting of ideas or associations, and *not* a splitting of personalities or multiple personalities, a common misconception in the public.

SZ affects approximately 24 million people worldwide, and 1% of Americans. It is considered the third most disabling condition after quadriplegia and dementia, and three-quarters of people with schizophrenia (PSZ) develop the disorder between the ages of 16 and 25 (Mueser & McGurk, 2004). Thus, not only is SZ widespread and debilitating, but it strikes at a critically important time in people's lives, when they are just entering society as adults.

The diagnosis of SZ is based upon the occurrence of combination of the two main types of symptoms suffered by people with the disorder: positive symptoms (including hallucinations, delusions and disorganized behavior or speech) and negative symptoms (including negative or flat affect, poverty of speech and movement, the lack of motivation and the inability to experience pleasure), along with social or occupational dysfunction occurring over a significant duration of time. Although typical and atypical antipsychotic medications used to treat SZ target the positive, and to some extent the negative symptoms, it is the cognitive symptoms, including cognitive impairment, that are the most strongly associated with functional outcome (e.g., social and occupational success; Green, 1996).

Cognitive impairment affects up to 75% of PSZ (O'Carroll, 2000). Neuropsychological abnormalities pre-date the development of SZ (O'Carroll, 2000), and in the initial prodromal phase (the pre-psychotic period preceding the first onset of the disorder), cognitive symptoms are the best predictor of developing full-blown SZ (Green, 1996). Further, in stabilized diagnosed patients, cognitive symptoms (as compared to positive or negative symptoms) are the best predictor of functional outcome (O'Carroll, 2000; Green, 1996). Thus, cognitive impairment may be a central and rate-limiting feature of the disorder.

Disturbances in executive functioning, including deficits in working memory (WM), long term memory, and cognitive control, are the hallmark cognitive symptoms associated with SZ. The focus of this dissertation is changes in the ability to use cognitive control (the ability to flexibly and adaptively guide and control behavior, depending on current goals) to both control what information gets into mind, and to filter unwanted information out of mind, in PSZ. To this end, two main question were asked:

First, is cognitive control impaired globally, or are only certain aspects of cognitive control impaired in SZ? The Context Model of cognitive deficits in SZ (Cohen & Servan-Schreiber, 1992) stipulates that cognitive deficits all result from a common information-processing deficit (a disturbance in the internal representation of context) which, in turn, may be explained by a single biological abnormality (a reduction of dopaminergic activity in prefrontal cortex). However, recent work by Friedman and Miyake (2004) and Nee, Wager and Jonides (2007) suggests that there are qualitatively different types of control processes, controlled by different brain systems, and that only some of these are impaired in SZ. In Chapters 1 and 2, the results of two studies that use

the control over the contents of WM (both filtering information perceptually, before it has entered WM, and inhibiting irrelevant information once it's already in WM) are presented to answer this question.

Second, does the nature of the information affect cognitive control? In healthy controls (HC), brain systems have evolved that select salient stimuli (signaling potential dangers and rewards) and organize appropriate behavioral responses (Taylor, Phan & Liberzon, 2005). For example, emotional information is facilitated and prioritized when attention is limited (Burke, Heuer & Reisberg, 1992), the presentation of emotionally arousing stimuli leads to enhanced memory for central details (Anderson & Phelps, 2001), and emotional arousal appears to increase the likelihood of memory consolidation (LaBar & Phelps, 1998). However, a core symptom in SZ is disruption to normal emotions and emotional responses (i.e., negative symptoms). Therefore, PSZ may not organize appropriate behavioral responses to salient stimuli that signal potential dangers and rewards in the same way as HC. Indeed, a recent meta-analysis across a wide range of tasks found that PSZ have deficits in processing emotional information, including emotion recognition, differentiating between emotions, and emotional face perception (Kohler, Walker, Martin, Healey & Moberg, 2010). Chapter 3 presents data from a study that measured the performance of PSZ and HC on a cognitive task in which emotionally expressive faces must be ignored, in order to answer this question.

Chapter 1

Intact and Impaired Cognitive Control Processes in Schizophrenia

Among the most frequently noted cognitive deficits in SZ are those involving cognitive control (Barch, 2005; Barch et al., 2004; Bellgrove et al., 2006; MacDonald et al., 2005). Discussions of these deficits often assume that there is a single attentional/ inhibitory deficit that leads to widespread consequences, as in the "Context model" of cognitive control (Barch, 2005; Cohen & Servan-Schreiber, 1992; Minzenberg et al., 2009). In this model, a deficit in a *unitary attention system*, mediated by the dorsolateral prefrontal cortex (DLPFC), is responsible for deficits in many tasks, including the Stroop, the AX-CPT, and language production tasks. In contrast, following the lead of recent work in cognitive neuroscience (Friedman & Miyake, 2004; Nee et al., 2007), we propose that there are qualitatively different kinds of control processes, only some of which are impaired in SZ. We provide evidence for this hypothesis by showing that PSZ are relatively intact in selecting perceptual information before entry into WM, but impaired in selecting information once in WM.

Nee and Jonides (2008, 2009) recently developed a pair of tasks called "Ignore" and "Suppress" that target cognitive control processes at different stages: perceptual selection versus selection in WM. Both tasks are variants of the Item-Recognition task (Sternberg, 1966), in which a memory set containing a few items is presented, followed by a brief delay, and then a probe to which the participant responds positively if it matches an item in the memory set, and negatively otherwise. In both the Ignore and Suppress tasks, the items in the memory set are words presented in two different colors (red and blue). In Ignore, just *before* the memory set is presented the participant is

instructed to attend to items of a particular color (e.g., the red ones), and consider only the items still in WM when responding to the probe. In Suppress, the participant is instructed to remember items of a particular color *after* the memory set is presented and consider only these items when responding to the probe. In both tasks, when a word that should have been ignored or suppressed is presented as the probe, or when the probe had not occurred in the memory set at all, a negative response is required. Thus, the Suppress task requires selection in WM, whereas the Ignore task promotes selection before items enter WM.

In both tasks the critical contrast is between performance on two kinds of negative probes: (1) "Lures", to which the participant should respond "No" because it was word that was in the original memory set but should have been intentionally ignored or suppressed; and (2) "Controls", to which the participant should respond "No" because it was a word that was not in the memory set. If selection were perfect there should be no difference between performance on Lure and Control probes; to the extent selection is poor, the difference between the two kinds of negatives will be large. More specifically, to the extent that selection is poor, a Lure probe will appear familiar, and participants will have to inhibit the tendency to respond positively on the basis of familiarity, which will lengthen reaction times (RTs; Monsell, 1978; Smith & Jonides, 1998). Nee and Jonides (2008) found that, with college students, RTs for Lures were longer than those for Controls, more so in the Suppress task than the Ignore task. This difference between the two tasks could not be attributed to the Suppress task being more difficult since the two tasks had equal RTs and error rates for Valid and Control trials, trials on which cognitive control was not needed. Further, Nee and Jonides (2008, 2009) used functional Magnetic

Resonance Imaging (fMRI) to image their participants while they performed the two tasks and found a neural dissociation between them: the ventrolateral prefrontal cortex (VLPFC) was recruited *only* during WM selection (Suppress), whereas the frontal eye fields were preferentially activated during perceptual selection (Ignore). The results imply that two qualitatively different processes are involved.

These findings give us a way to test our hypothesis that PSZ should be more impaired in WM selection than perceptual selection. One reason for this hypothesis is that the Suppress task is more dependent on the VLPFC (and DLPFC) than is the Ignore task (Nee & Jonides, 2008, 2009), and these areas are known to be dysfunctional in SZ (Callicott et al., 2003; Perlstein et al., 2001). Another reason is that PSZ are particularly impaired on WM tasks that require operating on stored information (e.g., Barch & Smith, 2008).

Methods

Participants

Participants included a total of 24 HC and 17 PSZ. Another 5 PSZ and 9 HC were tested but not included in the analysis because they either did not respond on more than 20% of trials, or had an error rate 2 standard deviations above the group average in one of the task conditions. The demographics of the two groups are shown in Table 1, along with clinical ratings for the PSZ.

HC, matched for age and education with PSZ, were recruited through local and online advertisements. They were free of current or past psychiatric or neurological illness, did not report alcohol or substance dependency in the last six months, and had no history of psychotropic medication use, such as antipsychotics/antidepressants. PSZ were

recruited through the Lieber Center Outpatient Clinic of the New York State Psychiatric Institute (NYSPI) and met DSM-IV criteria for SZ (N=14) or schizoaffective disorder (N=3). Diagnoses were determined through a diagnostic conference that included information from the Diagnostic Instrument for Genetic Studies (DIGS; Nurnberger et al., 1994), administered by trained research personnel and a thorough chart review. In addition, the Brief Psychiatric Rating Scale (BPRS; Overall, 1975), the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen & Olsen, 1982), and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen & Olsen, 1982) were used to evaluate symptom severity (Table 1).

	PSZ	HC
Variable		
N	*17*	*24*
Age (in years)	38.2 (11.11)	34.04 (8.43)
Gender (M/F)	8/9	15/9
Handedness		
Right	16	20
Left	1	4
Ambidextrous	0	0
Education (in years)	16.0 (2.24)	16.08
Age of Onset	23.6 (8.16)	
SANS		
Affective Flattening/5	.6 (.97)	
Alogia/5	.4 (.84)	
Avolition/Apathy/5	1.4 (1.84)	
Asociality/ Anhedonia/5	2.1 (1.45)	
SAPS		
Hallucinations	1.63 (2.26)	
Delusions	1.5 (1.41)	
Bizarre behavior	.75 (1.17)	
Thought Disorder	.5 (.97)	
Trails		
A	30.88 (6.86)	
B	66.63 (12.55)	
Wisconsin Card Sorting (% Error)	14.57 (8.93)	
Perseverations	7.45 (5.14)	
Non-Perseverations	7.45 (4.29)	
WAIS-R		
Verbal	113.71 (11.97)	
Performance	104.63 (19.92)	
Perceptual Organization	107.71 (18.24)	

Table 1. Demographics and clinical ratings of Healthy Controls (HC) and People with Schizophrenia (PSZ)

PSZ had been stabilized on antipsychotic medication for at least three months before the day of testing. A total of 15 PSZ were treated with atypical antipsychotics (e.g., abilify/aripriprazole), and 2 PSZ with a typical antipsychotic (haloperidol). All PSZ

were clinically rated (ratings were obtained between 2 weeks and 6 months from the testing day for 10 PSZ and more than 6 months but less than 1 year for 7 PSZ).

After the procedure was fully explained, written informed consent was obtained from all participants. The research protocol was approved by the Institutional Review Board of the NYSPI. Both PSZ and HC were English-speaking.

Procedure

Every participant was tested on both the Ignore and Suppress tasks. In the Ignore task (Figure 1A), the participant first saw an instruction to ATTEND to words of a particular color (red on half the trials, blue on the other half), then 1 sec later saw a 4-word memory set for 4.5 sec, then 3 sec later saw a probe word. The participant was instructed to respond positively if the probe matched either of the words that were supposed to still be in WM (POOL and TILL in Fig. 1A), and negatively otherwise. Responses were made by pressing either the 0 key (labeled "NO") to indicate a negative response, or the 1 Key (labeled "YES"), to indicate a positive response. On 40% of the trials the probe matched one of the words that should still have been in WM (TILL in Fig. 1A; Valid probes); on 30% of the trials the probe matched one of the words that should have been ignored and hence required a negative response (RATE in Figure 1A; Lure probes), and on the remaining 30% of the trials the probe did not match any word presented on that trial (HEAT in Fig. 1A; Control probes).

In the Suppress task (Fig. 1B) the participant first saw the 4-word memory set for 4.5 sec, and then 1 sec later saw an instruction to REMEMBER only the words of one color (red or blue). The rest of the trial events--including the three types of probes--were the same as in the Ignore task, except that the interval between the instruction and the

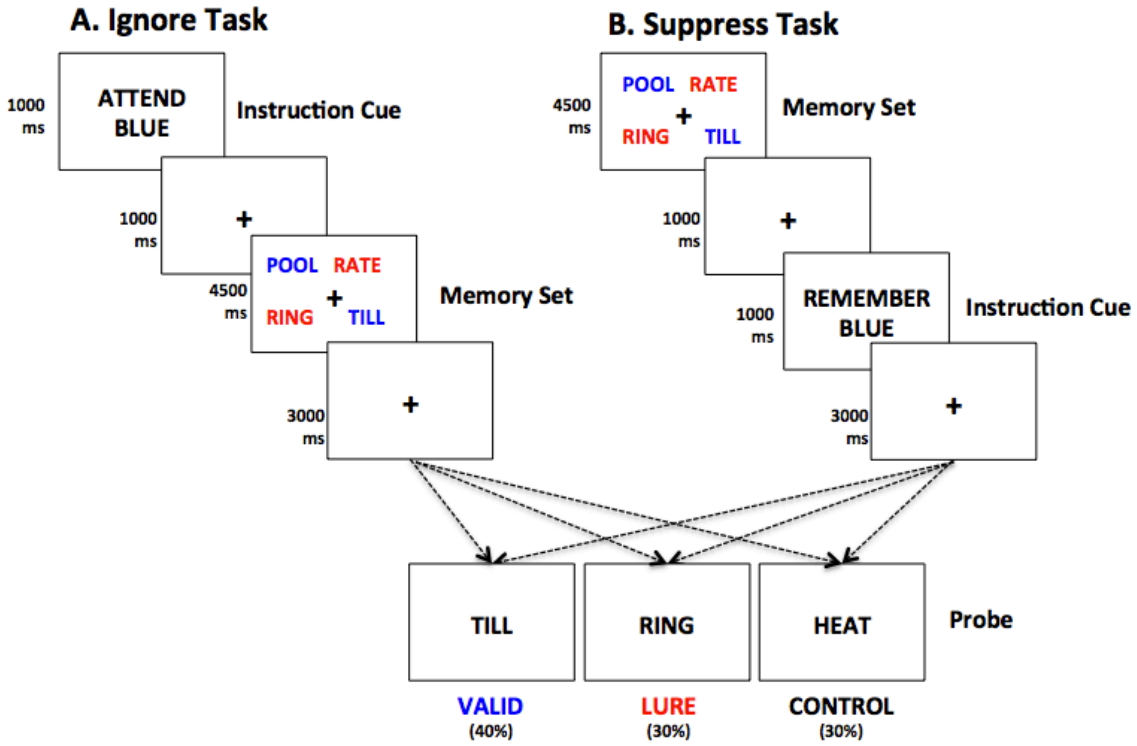


Figure 1. Ignore and Suppress Task Schematics

probe was shorter in order to keep the overall length of the trial equivalent across the two tasks. The major difference between Ignore and Suppress was when the critical instruction cue was given relative to the memory set; when the instruction cue occurred before the memory set--in Ignore--selection could occur on perceptual representations prior to entry into WM, whereas when the instruction cue was given after the memory set--in Suppress--selection could occur only in WM.

Trials were blocked by task, with 25 trials per block, including, on average, 10 Valid trials, 7.5 Control trials, and 7.5 Lure trials. There were 4 blocks each of Ignore and Suppress trials, yielding 30 observations per participant for each of the two kinds of negatives trials for each task. Participants completed at least two practice blocks, one each of Ignore and Suppress, before beginning the experiment. Ignore and Suppress task

blocks alternated, with the order of the blocks counterbalanced across participants. Feedback was given on practice trials but not experimental trials.

Materials

The words used were drawn from a set of 80 4-letter nouns.

Results

The data of major interest were the mean RTs for correct trials. For each participant, trials on which RTs were 2.5 standard deviations from their individual mean in each condition were excluded from the analysis (an average of 6.6 trials for both HC and PSZ). The resulting mean RTs, and the accompanying error rates, are presented in Table 2, separately for the Ignore and Suppress tasks. For each task, the data are organized by group (HC versus PSZ) and Trial-Type (Valid, Control, Lure).

We performed a 3-way ANOVA on RT with 1 between-participant factor (Group), and 2 within participant factors, Task (Ignore, Suppress) and Trial-Type (Lure, Valid, Control). There were main effects of all three factors--RTs were slower for: PSZ than HC [Group effect: $F(1, 39)=9.69$, $p=.003$]; Suppress than Ignore [Task effect: $F(1,39)=22.3$, $p=.000$]; and Lure than either Control or Valid [Trial-Type effect: $F(2, 78)=52.8$, $p=.000$.] Importantly, there was a significant three-way interaction [$F(2, 78)=4.22$, $p=.02$)], indicating that the contrast between Trial-Type was greater for PSZ than HC, but only in the Suppress task.

Overall, RTs for PSZ were substantially longer than those for HC but our hypothesis focuses on *difference-scores* between the two kinds of negatives (Lure vs. Control) as the main index of selection processes. The means and standard deviations of the RT difference-scores are in the last column of Table 2.

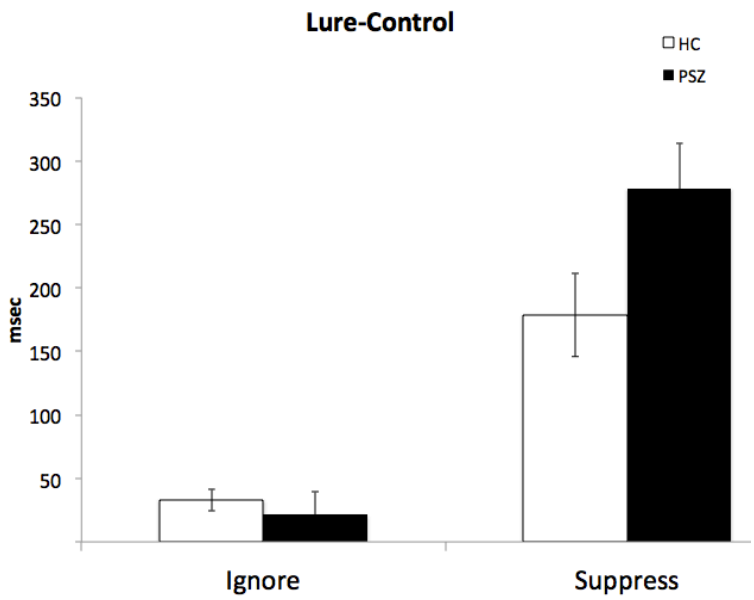
Reaction Time (msec)									
		Valid		Control		Lure		Lure-Control	
		MEAN	*SD*	*MEAN*	*SD*	*MEAN*	*SD*	*MEAN*	*SD*
Ignore	HC	738	179	708	174	741	189	33	44
	PSZ	941	272	937	246	959	266	21	74
Suppress	HC	731	215	720	195	898	311	179	162
	PSZ	909	254	934	259	1213	346	278	146
Error Rate (%)									
		MEAN	*SD*	*MEAN*	*SD*	*MEAN*	*SD*	*MEAN*	*SD*
Ignore	HC	3.1	4.0	.7	2.0	1.9	4.0	1.2	2.0
	PSZ	2.4	3.0	.6	1.0	2.3	3.0	1.6	4.0
Suppress	HC	5.5	4.0	1.8	4.0	6.1	7.0	4.3	5.0
	PSZ	6.5	7.0	2.6	9.0	7.8	8.0	5.3	13.0

Table 2. Reaction Times and Error Rates for Healthy Controls (HC) and People with Schizophrenia (PSZ) in the Ignore and Suppress Tasks

In Ignore, the difference-score is roughly the same for HC and PSZ (33 vs. 21 msec, respectively), whereas in Suppress the difference-score is substantially greater for PSZ than HC (278 vs. 179 msec, respectively). The error-rate difference-scores show a similar pattern (Ignore: PSZ=1.6 vs. HC=1.2; Suppress: PSZ=5.3 vs. HC=4.3). These results suggest that, compared to HC, PSZ are differentially impaired on the Suppress task, which in turn implies that people have a specific deficit in selecting information in WM, *not a general attention deficit*.

The above observations are supported by a 2-way ANOVA on the RT difference-scores. The ANOVA had 1 between-participant factor (Group) and 1 within-participant factor (Task). RT difference-scores were larger in Suppress than Ignore (F (1, 39) = 77.12, $p < .001$)--but there was no Group effect (F(1,39)=2.29, p=.14). Importantly, there was a significant two-way interaction: PSZ showed a greater RT difference-score than HC on Suppress but not on Ignore ($F(1, 39) = 5.84$, $p = .02$ (Figure 2)).

Post-hoc 2-tailed t-tests revealed a significant difference between PSZ and HC in Suppress (t (39) = -2.02, $p = .05$), but not in Ignore ($t(39) = 0.27$, *ns)*. The critical two-



way interaction remains marginally significant even when each RT difference-score is normalized by dividing it by the RT for Control trials ($F(1,39) = 3.50$, $p = .07$), which removes any confounding due to base RT.

Figure 2. Reaction Time Difference-Scores (Lure-Control) in the Ignore and Suppress Tasks for Healthy Controls (HC) and People with Schizophrenia (PSZ)

This is evident in Figure 3, which shows difference-scores for the 17 highest-ranking HC and all 17 PSZ, with the participants rank-ordered on the x-axis by magnitude of difference-score, separately for PSZ and HC; only one participant here failed to show a positive RT difference-score, and difference scores were always higher for PSZ than for comparable HC.

A comparable ANOVA for error-rate difference-scores revealed only that there was a larger overall difference-score in Suppress than Ignore ($F(1,39) = 5.37$, $p=.03$).

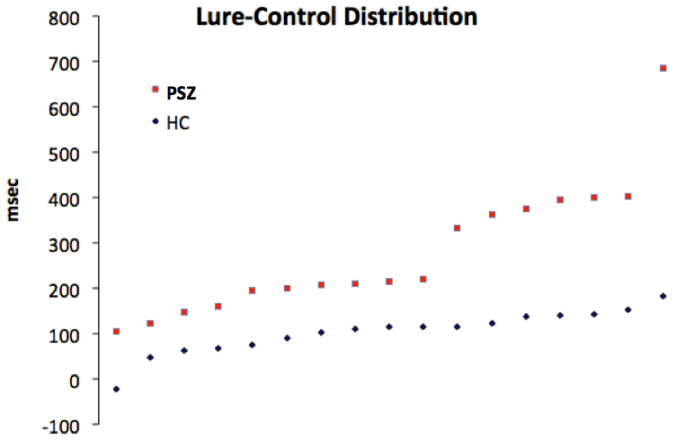


Figure 3. Reaction time (RT) Difference-Scores in Suppress for all People with Schizophrenia (PSZ) and the 17 highest ranked Healthy Controls (HC); The participants are ordered on the x-axis by the magnitude of their RT Difference-Scores.

Discussion

Relation to other Findings

Our findings support the hypothesis that PSZ are impaired when they have to select information from WM but not when they have to select perceptual information. The latter finding fits with the results of Gold et al. (2006). In their tasks, participants were cued about which of two locations was likely to contain a target object that required a response; PSZ performed as well as HC (for a qualification, see Hahn et al., 2010). Our Ignore task is similar to the Gold et al. tasks in that the participant can use the color of the words to direct attention to the critical locations. Our finding that PSZ are impaired in selecting information in WM also fits with previous findings. The task that has been most frequently used to study WM deficits in SZ is the N-back, in which the participant is presented a sequence of items and for each one must decide whether it is identical to the one N back in the sequence. When N=2 or 3, PSZ show a deficit that is often attributed to the updating demands of the task (Manoach, 2003; Perlstein et al., 2001); e.g., when N=2, after making his/her response on a trial the participant must "drop" the item in WM that occurred 2 back in the sequence. The latter process seems the same as the intentional forgetting in our Suppress task, so the deficit in N-back may reflect faulty selection in WM.

Issues about Difficulty

What about the possibility that what makes the Suppress task difficult for people is not a deficit in WM selectivity, but rather a deficit in WM capacity? The PSZ's limited capacity could have been exceeded by four words plus their color associations (see Figure 1B). However, if exceeding WM capacity was the real problem for PSZ in the

Suppress task, there should have been a difference between PSZ and HC on *every trial type*, as the large WM load occurs on every trial type. However, there was no error rate difference between PSZ and HC on Control trials (see Table 2), and the largest RT difference between PSZ and HC occurred on Lure trials, which is when memory selectivity is required (see Figure 1).

A related concern is that PSZ may have been impaired in Suppress but not Ignore because Suppress was a more difficult task. In the Introduction we argued that, based on studies with college students, the two tasks were of equal difficulty because there was no difference between them in RTs or error rates on Valid or Control probes (Nee & Jonides, 2008, 2009). But in our experiment the error rate was significantly higher for Suppress than Ignore on both Valid and Control trials (see Table 2). In view of this finding, for the Suppress task we performed a subsequent analysis on a subset of 10 PSZ and 13 HC who were highly accurate on Valid and Control trials (<7% errors), and who were closely matched on these error rates (e.g., for Suppress Valid trials, the error rates for PSZ and HC were 5.25 and 5.37). Given that this was not a planned comparison, we used a Bonferroni correction for multiple comparisons, 2 in this case (i.e., we used a *p* value of .05/2). The RT difference-scores for this subset of participants mimicked our findings with the full set of data: these difference-scores were not significantly different between PSZ and HC in Ignore (37 vs. 19 msec, respectively, t(21)=-.71, *ns*), but they were significantly different in Suppress (261 vs. 132 msec, respectively, t(21)=-2.32, p=.03).

Specificity of the Suppress Deficit in PSZ

The selection deficit in Suppress may be relatively specific to PSZ, as it does not occur with two other patient populations. We tested people with Obsessive Compulsive

Disorder (OCD) and matched HC on the same Ignore and Suppress tasks as described above, except that the memory set contained 6 rather than 4 words (Ahmari, Eich, Cebenoyan, Smith & Simpson, under review). We found no difference between RT difference-scores for people with OCD and HC in either Ignore or Suppress. Joormann et al. (2010) tested people with Major Depressive Disorder (MDD) and HC on comparable Ignore and Suppress tasks. When the items were neutral (letters), Joormann et al. found no difference between people with MDD and HC in the magnitude of the RT difference-scores in Ignore or Suppress. However, when the words were negatively valenced, the RT difference-scores in Suppress was greater for people with MDD than HC. Thus, for people with MDD the impairment in WM selection may be state-dependent, whereas for PSZ it may be trait-dependent.

Limitations

One potential problem with our study concerns our sample of PSZ: they were unusually highly educated (16 years of education on average—see Table 1), and they could even have been higher-functioning intellectually than the HC. But the latter supposition cannot explain why our PSZ were impaired only in the Suppress task. Another potential problem concerns our analysis of subsets of the PSZ and HC who were roughly equally accurate in both Ignore and Suppress task (see **Issues about Difficulty**). This analysis included only 10 PSZ and 13 HC. Clearly it would have been better to have a larger total sample, which would have permitted a larger number of participants to be included in the subsequent analysis.

Chapter 2

The neural correlates of impaired control over working memory in schizophrenia

Among the most frequently noted of the cognitive symptoms in SZ are deficits in WM (Silver, Feldman, Bilker & Gur, 2003; Goldman-Rakic, 1994; Tek, Gold, Blaxton, Wilk, McMahon & Buchanan, 2002; Lencz, Bilder, Turkel, Goldman, Robinson, Kane & Lieberman, 2003). WM is a complex construct comprised of component processes that enable the short-term retention of information in order to guide goal-directed behavior (Baddeley, Logie, Bressi, Della Sala & Spinnler, 1986; Jonides, Lewis, Nee, Lustig, Berman & Moore, 2008). WM supports a variety of cognitive abilities, including learning, reasoning, verbal comprehension and academic success (Kane & Engle, 2002), and might even be a better predictor of academic success than IQ (Alloway & Alloway, 2010). Due to its centrality in cognition, it is not surprising that WM deficits in SZ are associated with impairments in social and occupational functioning (Bowen, Wallace, Glynn, Nuechterlein, Lutzker & Kuehnel, 1994; Corrigan, Green & Toomey, 1994). Hence, understanding breakdowns in the component processes in WM in SZ is fundamental to understanding not only cognitive function in the disorder, but also the disorder itself.

Previous studies have provided the groundwork for addressing behavioral WM deficits in SZ. Deficits have been attributed to a failure in cognitive control over the inhibition of irrelevant information in WM or the selection of responses at retrieval (e.g., Barch, Carter, Perlstein, Baird, Cohen & Schooler, 1999; Barch, Carter & Cohen, 2004; MacDonald, Carter, Kerns, Ursu, Barch, Holmes, Stenger & Cohen, 2005; Cohen,

Dunbar, Barch & Braver, 1997; Callicott, Straub, Pezawas, Egan, Mattay, Hariri, et al., 2005; Perlstein, Carter, Noll & Cohen, 2001). However, prior approaches to studying WM in SZ have employed tasks requiring multiple cognitive control processes that are challenging to disentangle, making it difficult to determine which specific component processes are impaired (Cohen, Dunbar, Barch & Braver, 1997; Milham, Banich, Webb, Barad, Cohen, Wszalek & Kramer, 2001; Milham, Banich & Barad, 2003; Monchi, Petrides, Petre, Worsley & Dagher, 2001; Jonides & Nee, 2005; Fleming, Goldberg, Gold & Weinberger, 1995; Goldberg, Weinberger, Pliskin, Berman & Podd, 1989; Randolph, Gold, Carpenter, Goldberg & Weinberger, 1992). To help address this issue, we previously examined PSZ and HC in a task that dissociated two forms of cognitive control over WM (Smith, Eich, Cebenoyan, Malapani, 2011, Chapter 1). We compared the filtering of irrelevant distractors *before* items entered WM and the inhibition of irrelevant distractors *after* information had entered WM (Nee & Jonides, 2008; Nee & Jonides, 2009). We found that PSZ were unimpaired when they had to filter items before they entered WM, indicating intact encoding processes and ruling out a general WM deficit. Yet, the same people were impaired when they had to inhibit irrelevant distractors after information had entered WM. These data support the idea that WM deficits are not global in SZ. However, since the behavioral data could not examine ongoing processing, and only reflected the response to the probe, we could not determine whether the deficit was due to a failure to inhibit irrelevant information in WM or to interference control at retrieval.

In the current study, we used functional Magnetic Resonance Imaging (fMRI) to examine PSZ and HC during a single cognitive task that allowed us to separate the neural

mechanisms contributing to 1) the maintenance of information in WM prior to inhibitory demands, 2) the inhibition of irrelevant items from WM, and 3) the resolution of interference of irrelevant information at the time of retrieval. Thus, the design separated various phases of WM to investigate the precise subcomponents of WM that are impaired in PSZ, which ultimately lead to difficulties during retrieval.

Participants were first presented with a memory set consisting of two red and two blue words (see Figure 4). Thereafter, the four words were removed from view. This constituted the PreCue, maintenance-only phase of the task. Participants were then instructed, via an instruction cue, to retain only two of the words, corresponding to the instruction cue's color (e.g. blue), and to consider only these words when responding to the test probe. The PostCue phase measured inhibitory-control of items in WM. Here, participants should reduce their WM load by inhibiting memory representations of the two irrelevant (e.g. red in fig. 4) words, retaining representation of only the two relevant (e.g. blue in fig. 4) words. Finally, in the third and final phase of the task, participants retrieved information from WM. A test probe required a positive response if it matched one of the two target words (Valid; e.g., either of the blue words in fig. 4) and a negative response if it either matched a word that should have been inhibited (Lure; e.g. either of the red words in fig. 4), or if it had not been presented in the trial (Control).

We hypothesized that PSZ would be specifically impaired at inhibiting information in WM, reflected in the second phase of the task. The hypothesis makes the following predictions: in the maintenance-only portion of the task prior to the cue (PreCue), PSZ and HC should show equivalent neural activations in areas involved in

WM maintenance, particularly the posterior areas of the left VLPFC (BA (Broadmann Area) 44), thought to reflect phonological rehearsal (Smith & Jonides, 1998; Awh, Jonides, Smith, Schumacher, Koeppe & Katz, 1996). After the instruction cue (PostCue), HCs were predicted to show a reduction in maintenance-related activation in posterior VLPFC, which has been shown to vary linearly based on the verbal WM load (Smith & Jonides, 1998), due to the inhibition of irrelevant items. By contrast, activation in this area was predicted to remain elevated in PSZ commensurate with their inability to inhibit items from WM. These inhibitory failures in PSZ were expected to lead to increased interference during the third, retrieval-phase of the task. Here, we predicted that PSZ would have more difficulty in distinguishing Lures from Valid items. If Lure word representations were successfully inhibited from WM, performance on Lure probes should be equivalent to performance on Control probes. However, if items were not appropriately inhibited, then Lure probes would require additional interference-control processes to be distinguished from Valid probes. This difficulty was expected to be reflected in increased activation in the left mid-VLPFC (BA 45), an area associated with the resolution of WM-based conflict (Jonides & Nee, 2006). Hence, a deficit in inhibiting information in WM was predicted to lead a dynamic pattern of neural differences between PSZ and HC.

Methods

Participants

Data from 18 HC and 18 PSZ are reported. Demographics are shown in Table 3, along with clinical ratings for the PSZ. Another 4 PSZ and 4 HC were tested but not

included in the analysis because they did not respond on more than 20% of trials or had an error rate of 2 standard deviations above the respective group average in one of the probe-type conditions. HC, matched to PSZ for gender, age and education were recruited through local and online advertisements. They were free of current or past psychiatric or neurological illness, did not report alcohol or substance dependency in the last six months, and had not used psychotropic medication, such as antipsychotics or antidepressants, in the last year. PSZ were recruited through the Lieber Center for Schizophrenia Research and Treatment of NYSPI and all PSZ met DSM-IV criteria for SZ (First, Spitzer, Gibbon & Williams, 2007). Diagnoses were determined through a diagnostic conference that included information from either the DIGS (Nurnberger, Blehar, Kaufmann, York-Cooler, Simpson, Harkavy-Friedman, *et al,* 1994) or the SCID (First & Pincus, 2002). Additionally, the SAPS and SANS (Andreasen & Olsen, 1982) and the Calgary Depression Scale (Addington, Addington, Maticka-Tyndale & Joyce, 1992) were used to evaluate symptom severity. Ratings were obtained between 2 weeks and 2 months from the testing day for 10 PSZ and more than 2 months but less than 5 months for 8 PSZ. All PSZ were being treated with atypical antipsychotic medication for at least three months, and had taken the same type and dose of medication

	PSZ	HC
Variable		
N	*18*	*18*
Age (in years)	37.9 (9.3)	36.3 (8.2)
Gender (M/F)	7/11	5/13
Handedness		
Right	17	17
Left	1	1
Ambidextrous	0	0
Education (in years)	14.3 (2.4)	15.6 (2.0)
SANS		
Affective Flattening/5	2.00 (1.14)	
Alogia/5	0.83 (1.42)	
Avolition/Apathy/5	1.71 (1.40)	
Asociality/ Anhedonia/5	2.39 (1.42) / 5	
SAPS		
Hallucinations	1.17 (1.76)	
Delusions	1.22 (1.40)	
Bizarre behavior	1.06 (1.30)	
Thought Disorder	0.72 (1.23)	
Calgary Depression	2.61 (2.28)	

Table 3. Demographics and clinical ratings of Healthy Controls (HC) and People with Schizophrenia (PSZ)

for at least one month before the day of testing. All participants were English-speaking. All but two participants (one person with SZ, one healthy control) were right handed.

After the procedure was fully explained, written informed consent was obtained. Capacity to participate in the experiment was also assessed for each patient via an interview process with a psychiatrist not related to the study. The research protocol was approved by the Institutional Review Board of the NYSPI and Columbia University.

Procedure

Participants were presented with a 4-word memory set for 4000ms and were instructed to retain the items in memory (Figure 4). Two of the words were presented in red and the other 2 were in blue. The PreCue phase consisted of a 6000-8000ms retention-interval following the memory set presentation. Thereafter, an instruction cue, presented for 2000ms, told participants to retain in memory only the words of one color (red on half the trials, blue on the other half). The PostCue WM retention-interval was 6000-8000ms.

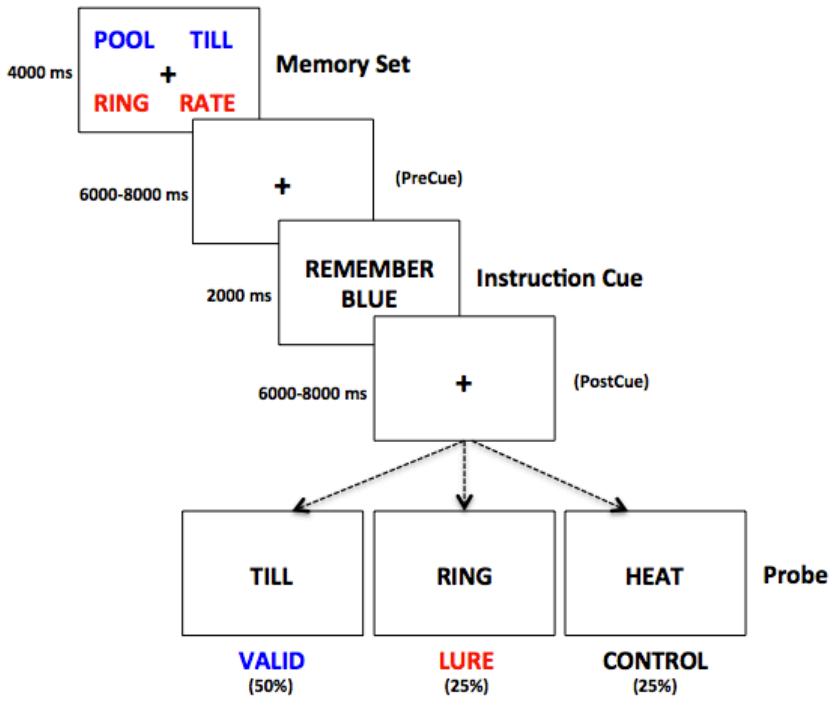


Figure 4. Suppress fMRI Task Schematic

Then, participants were presented with a probe word requiring an positive response if the probe matched either of the words that should have been retained in WM (e.g. POOL and TILL), and negative response otherwise. All responses were made using the non-dominant hand with a middle finger press indicating a negative response and an index finger press indicating a positive response. On 50% of the trials the probe matched one of the words that should have been in WM (Valid probes); on 25% of the trials the probe matched one of the words that should have been inhibited from WM (Lure probes), and on the remaining 25% of the trials the probe did not match any word presented on that trial (Control probes). Control probes were restricted to stimuli that had not appeared for at least 3 subsequent trials in order to minimize effects of proactive interference. Participants completed 8 blocks of 12 trials each. Feedback was given on practice trials, completed outside of the scanner, but not on experimental trials. Experimental tasks were presented using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) and the Current Designs HH2x4-C system, with its 4-button response unit. Stimuli were projected onto a mirror above participant's eyes that was attached to the head coil.

Materials

The stimuli consisted of 80 four-letter nouns that have been used in previous studies with this paradigm (Nee & Jonides, 2008; Nee & Jonides, 2009; Smith, Eich, Cebenoyan & Malapani, 2011).

fMRI Data Acquisition

Whole-brain imaging was conducted using a SENSE head coil on a 3.0T Phillips fMRI system located at Columbia University's MRI Research Center. Head padding was

used to minimize head motion; subsequent inspection showed that no participant's motion exceeded 2 mm in any direction from one volume acquisition to the next. Structural images were collected using a high-resolution T1-weighted MPRAGE pulse sequence (1 X 1 X 1 mm voxel size). Functional images were collected using a gradient echo T2*-weighted echoplanar (EPI) sequence with blood oxygenation level-dependent (BOLD) contrast (TR = 2000 ms, TE = 20 ms, flip angle = 77, 3 X 3 X 2 mm voxel size; 52 contiguous axial slices). For each functional scanning run, five discarded volumes were collected prior to the first trial to allow for magnetic field equilibration.

Imaging Preprocessing and Analysis

Functional data were spike-corrected to reduce the impact of artifacts using AFNI's 3dDespike (http://afni.nimh.nih.gov/afni). Subsequent processing and analyses were done using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Functional images were corrected for differences in slice timing using sinc-interpolation, and head movement was corrected using a least-squares approach and a 6 parameter rigid body spatial transformation. Structural data were coregistered to the functional data and segmented into gray and white-matter probability maps (Ashburner & Friston, 1997). These segmented images were used to calculate spatial normalization parameters to the MNI template, which were subsequently applied to the functional data. As part of spatial normalization, the data were resampled to 2 x 2 x 2 mm. An 8-mm full-width/half-maximum isotropic Gaussian smoothing kernel was applied to all functional images prior to analysis using SPM5. All analyses included a temporal high-pass filter (128 s),

correction for temporal autocorrelation using an autoregressive AR(1) model, and each image was scaled to have a global mean intensity of 100.

fMRI Analysis

Univariate analyses were conducted using the general linear model implemented in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Regressors-of-interest included the WM maintenance period prior to the cue (PreCue), the WM maintenance period following the cue (PostCue), and the retrieval probe. Maintenance-related regressors spanned the length of the maintenance interval while probe-related regressors were modeled as an impulse. Separate probe-related regressors were included for each probe type (Valid, Control, Lure). Events from trials in which an error occurred were modeled separately and were excluded from subsequent analyses. Two 16 second fixation periods were included in each run that were modeled with a separate regressor that served as a measure of baseline activation. Additional nuisance regressors were included to capture activation related to encoding and the cue. All of the regressors described above were convolved with a canonical hemodynamic response function.

Ventrolateral Prefrontal Cortex Regions-of-Interest

Two contrasts of interest were estimated for each participant. The first examined WM maintenance-related activation by contrasting PreCue – PostCue. The second examined interference-control processes at retrieval by contrasting Lure – Control trials. Contrast images for each participant were submitted to second-level 2-sample t-tests.

To identify regions involved in WM-maintenance and interference-control, we performed whole-brain analyses collapsing across group. Given previous demonstrations of the role of the left posterior-VLPFC in WM maintenance (Smith & Jonides, 1998) and left mid-VLPFC in interference-control (Nee & Jonides, 2008, 2009; Smith & Jonides, 1998; Awh, Jonides, Smith, Schumacher, Koeppe & Katz, 1996; Jonides & Nee, 2006; Jonides, Smith, Marshuetz, Koeppe & Reuter-Lorenz, 1998; Nee, Jonides & Berman, 2007), we focused brain-brain and brain-behavior relationship analyses on the left VLPFC. Each region was defined anatomically and then data from voxels showing significant activation in the whole-brain analyses was extracted. The left posterior VLPFC was defined as the left inferior frontal gyrus, pars opercularis and the left mid-VLPFC was defined as the left inferior frontal gyrus, pars triangularis according to demarcations provided by the Anatomical Automatic Labeling atlas implemented by WFU pickatlas (Tzourio-Mazoyer, Landeau, Papathanassiou, Crivello, Etard, Delcroix, *et al*, 2002).

Group differences in the VLPFC were examined in two ways: first, we examined group differences averaging across all voxels demonstrating a significant effect in whole-brain analyses that collapsed across group. These analyses were thresholded at $p < 0.001$ at the voxel-level with a 74 voxel cluster extent providing correction for multiple comparisons ($p < 0.05$ family-wise error corrected) according to simulations with AlphaSim. Areas demonstrating significant activation were subsequently tested for group differences. Since these regions were identified through analyses that collapsed across group, these areas provide unbiased estimates for examining group differences. For

completeness, whole-brain analyses are reported separately for each group, as well as whole-brain group differences (see Supplemental Tables 1-3).

Second, heterogeneity within the VLPFC was explored by separately examining spherical ROIs centered around each peak in the VLPFC reported in the whole-brain analyses that collapsed across group. In this latter analysis, five peaks within left posterior VLPFC and three peaks within left mid-VLPFC were explored with the restriction that each peak was separated from all other peaks by at least 7mm. Each spherical ROI had a 5mm radius. These criteria resulted in each ROI being separated by other ROIs by at least a single voxel. Follow-up analyses exploring brain-brain and brain-behavioral relationships were estimated in the left posterior-VLPFC and mid-VLPFC spheres demonstrating maximal group differences. The left posterior VLPFC ROI was centered around (-50, 8, 22) and the left mid-VLPFC ROI was centered around (-40, 32, 22).

We used the Lure – Control difference in error rate as a behavioral metric of interference-control. Neural effects assessed the PreCue – PostCue and Lure – Control contrast. Relationships were tested using robust regression, which is more robust to outliers than other correlation methods (Wager, Keller, Lacey& Jonides, 2005).

Results

Behavioral Performance

The data of interest were the mean error rates and the reaction times for correct trials (Valid, Control and Lure). For each participant, trials on which reaction times were

±2.5 standard deviations their individual mean in each probe-type condition were excluded from the analysis (mean 2.25 trials for HC; 2.43 for PSZ).

Separate repeated measures ANOVAs with Probe-Type as a within-subjects variable, and Group (HC or PSZ) as a between-subjects variable were computed for error rates and RTs. For error rate, there was a significant main effect of Probe-Type ($F(2, 68)=27.1$, $p<.001$) and a significant main effect of Group ($F(1, 34)=15.3$, $p<.001$), such that the PSZ made more errors than HC. Critically, there was a significant interaction between Probe-Type and Group ($F(2, 68)=5.7$, $p=.005$). While PSZ made more errors than HC in all three Probe-Types [Valid ($t(34)=3.46$, $p=.001$; 18.1 (13.5) vs. 5.9 (6.6); Lure ($t(34)=3.76$, $p=.001$, 18.15 (13.54) vs. 5.88 (6.58); and Control ($t(34)=2.27$, $p=.03$; 5.19 (8.2) vs. 0.72 (1.64)], PSZ made significantly more errors to Lure probes compared to Control probes relative to HC ($t(34)=-2.9$, $p=.007$; Figure 5). This replicates our previous finding that PSZ demonstrate a deficit in the Lure condition (Smith, Eich, Cebenoyan & Malapani, 2011, Study 1). PSZ also made more errors on Valid probes compared to Control probes relative to HC ($t(34)=-2.6$, $p=0.02$), suggesting that PSZ had difficulty distinguishing Valid from Lure probes.

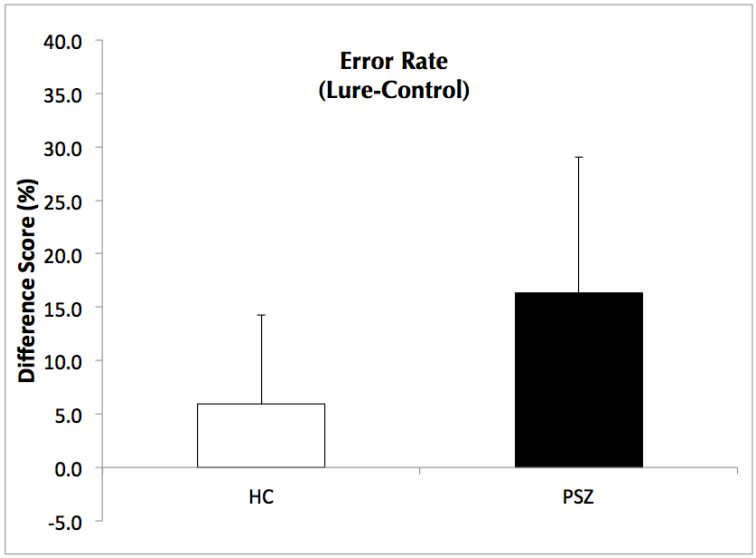


Figure 5. Error rate Difference-Scores (Lure-Control) for Healthy Controls (HC) and People with Schizophrenia (PSZ)

For RT, there was a significant main effect of Probe-Type ($F(2, 68)=62.2$, $p<.001$) and a significant main effect of Group ($F(1, 34)=20.82$, $p<.001$). PSZ were significantly slower than HC for all 3 Probes-Types (Valid: 1067.15 (273.8) vs. 709.4 (183.67); Lure: 1270.41 (295.79) vs. 886.71 (250.74); Control: 1043.3 (272.1) vs. 717.19 (156.67)). However, the Probe-Type x Group interaction was not significant ($F(2, 68)=.96$, *ns*). Planned between-group comparison of the Lure vs. Control RT difference was not significant ($t(34)=-1.28$, ns), although a trend towards PSZ exhibiting a greater difference score was evident.

fMRI Results

Maintenance and Inhibitory Control of WM

To isolate specific SZ deficits, we began by identifying areas involved in maintaining information in WM by contrasting PreCue and PostCue activations (Figure 6). This contrast measured a load effect (i.e. four items PreCue, two items PostCue) predicated on appropriate use of the cue to inhibit items from WM. Previous research has indicated that this assumption is valid in healthy young and older participants (Oberauer, 2001). As anticipated, the contrast revealed significant differences in the left posterior VLPFC consistent with known WM load-related effects in this region (Smith & Jonides, 1998; see Supplemental Table 1 for additional areas).

To examine whether PSZ demonstrated impaired control over WM, we compared left posterior VLPFC activation between HC and PSZ. Failure to inhibit irrelevant content from WM would be expected to reduce the difference between PreCue and PostCue activation in PSZ due to elevated PostCue activation. Averaging across

activation in the entire left posterior VLPFC cluster revealed by the whole-brain analysis above, HC demonstrated a robust PreCue > PostCue difference ($t(17) = 6.90$, $p < 0.00001$). PSZ showed a similar, albeit muted effect ($t(17) = 3.05$, $p < 0.01$).

Direct comparison between the groups revealed a significant interaction with a greater PreCue > PostCue difference in HC compared to PSZ ($t(34) = 2.39$, $p < 0.05$). To further interrogate this difference, we separately examined ROIs centered around each left posterior VLPFC peak revealed by the whole-brain analysis. While all portions of the left posterior VLPFC demonstrated a numerical trend for a reduced PreCue > PostCue difference in PSZ relative to HC, a significant group difference ($t(34) = 2.48$, $p < 0.05$) was found in only a single region (center: -50 8 22; Table 4). In this region, whereas HC showed a significant PreCue > PostCue difference ($t(17) = 5.90$, $p < 0.0001$), PSZ did not ($t(17) = 1.29$, $p > 0.2$), resulting in a group difference ($t(34) = 2.48$, $p < 0.05$). While HC and PSZ showed similar PreCue activation ($t(34) = 0.28$, $p > 0.75$), PSZ showed significantly increased activation PostCue relative to HC ($t(34) = 1.72$, $p < 0.05$ one-tailed). This is consistent with the behavioral findings that PSZ demonstrate a failure to inhibit irrelevant items from WM (Figure 6).

PreCue-PostCue			
Peak	**HC**	**PSZ**	**HC vs PSZ**
-52 10 6	6.49***	2.03†	1.23
-54 8 16	4.75***	1.91†	1.25
-50 8 22	5.90***	1.29	2.48*
-52 16 22	4.71***	2.09†	1.71†
-50 12 28	4.49***	2.40*	1.69
Lure-Control			
Peak	**HC**	**PSZ**	**HC vs PSZ**
-48 24 22	1.71	4.42***	-2.28*
-40 32 22	0.31	4.45***	-3.12**
-38 16 22	2.22*	3.04*	-1.18

Table 4. Results in Ventrolateral Prefrontal Cortex

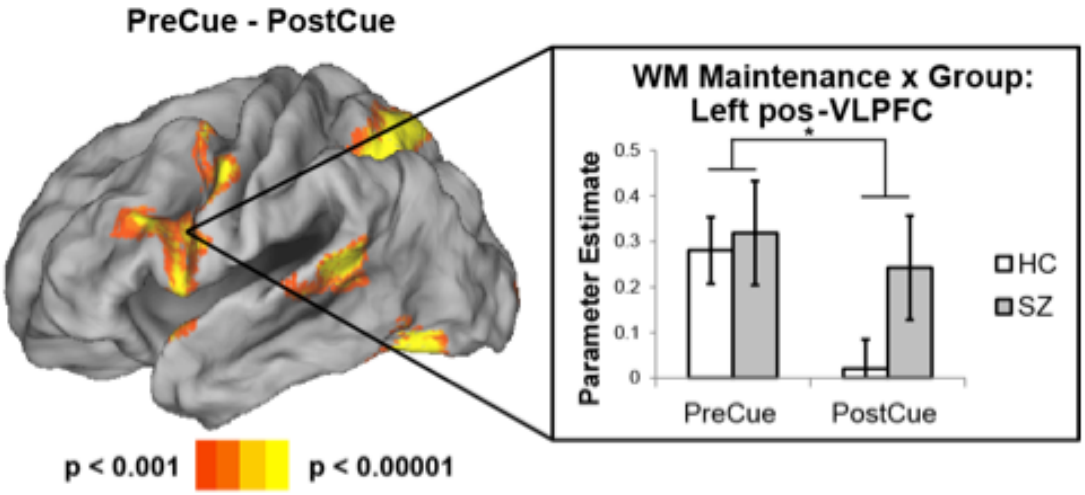


Figure 6. Maintenance and inhibition-related activations. Left: contrast of PreCue – PostCue maintenance activations collapsing across groups. Right: parameter estimates extracted from the left posterior ventrolateral prefrontal cortex (pos-VLPFC) averaged across a 5 mm sphere centered around -50 8 22. In this region, Healthy Controls (HC) and People with Schizophrenia (SZ) demonstrated equivalent PreCue activation. While HC's demonstrated reduced activation PostCue, SZ did not. These results indicate inhibition-related reductions in pos-VLPFC activation in HC's, but not SZ. * - p < 0.05.

Interference-Control at Retrieval

Next, we examined regions involved in interference-control, comparing probe-related activations for Lure probes to Control probes. Here, when collapsing across group, significantly greater activations were observed in the left mid-VLPFC for Lure probes relative to Control probes (Figure 7), consistent with the hypothesized role of this region in interference-control (27, 31, 33, 38; see Supplemental Table 2 for additional areas). In the analyses of maintenance epochs, we observed that PSZ showed impairments in inhibiting irrelevant content from WM. Such impairments should lead to increased demands on interference-control when responding to Lure probes. Thus, we predicted that PSZ would show increased Lure > Control activation than HC. Averaging

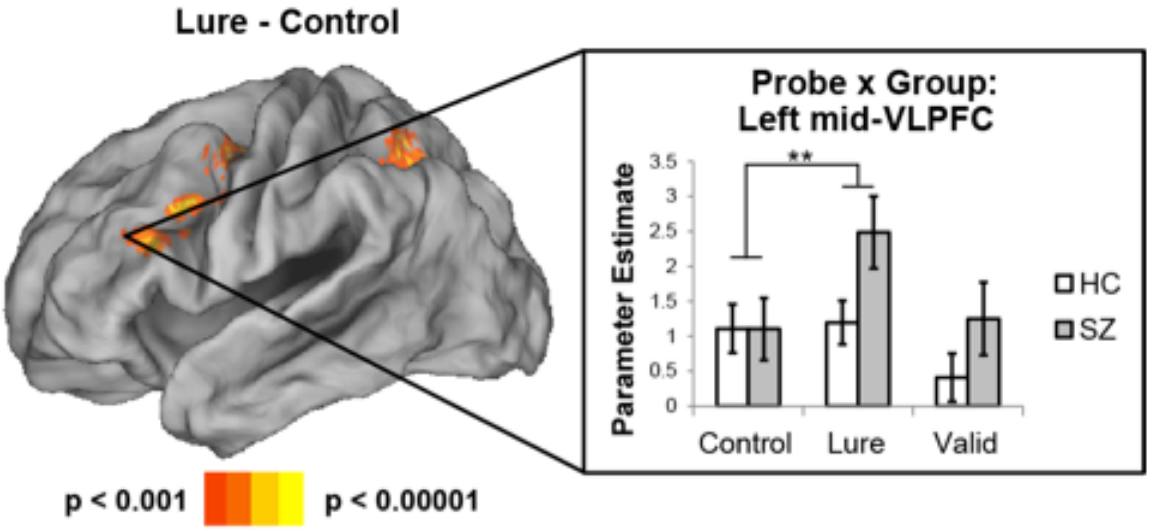


Figure 7. Interference-control related activations. Left: contrast of Lure – Control probe activations collapsing across groups. Right: parameter estimates extracted from the left mid ventrolateral prefrontal cortex (mid-VLPFC) averaged across a 5 mm sphere centered around -40 32 22. In this region, Healthy Controls (HC) and People with Schizophrenia (SZ) demonstrated equivalent activation to Control probes. However, activation was significantly elevated for Lure probes in SZ, but not HC's. These results indicate increased demands on interference-control to Lure probes in SZ. ** - $p < 0.005$

across the left mid-VLPFC cluster revealed by the whole-brain analysis described above, PSZ indeed demonstrated strongly increased activation for Lure probes relative to Control probes ($t(17) = 4.86$, $p < 0.0005$). By contrast, HC showed a weaker effect ($t(17) = 1.87$, $p < 0.05$ one-tailed). Direct comparisons between groups revealed a significant difference as PSZ showed a stronger Lure > Control effect than HC ($t(34) = 2.38$, $p < 0.05$). To further explore this difference, we separately examined ROIs centered around each left mid-VLPFC peak revealed by the whole-brain analysis. While no group difference was found in the posterior-most peak (-38 16 22: $t(34) = 1.18$, $p > 0.2$), group differences were progressively stronger as activations proceeded anteriorly (-48 24 22: $t(34) = 2.28$, $p < 0.05$; -40 32 22: $t(24) = 3.12$, $p < 0.005$). As depicted in Figure 7, in the anterior-most mid-VLPFC peak, HC and PSZ showed nearly identical activation to Control probes ($t(34) = 0.01$, $p > 0.99$), while PSZ showed significantly increased

activation to Lure probes ($t(34) = 2.18, p < 0.05$). These results suggest that PSZ require increased interference-control to Lure probes relative to HC, but are identical to HC when no interference-control is required.

Relationship Between Inhibition, Interference-Control, and Behavior

The data demonstrate differences between HC and PSZ in neural measures of inhibition and interference-control, and behavioral measures of performance. These measures are likely to be inter-related: impaired control over memory (manifested through inhibitory deficits PostCue) leads to the increased reliance on interference-control processes at the time of the probe. The strain on interference-control processes results in increased behavioral errors at retrieval. To explore this hypothesis, we examined the relationship between maintenance-related activations in the posterior VLPFC, interference-control related activations in the mid-VLPFC, and behavioral performance. To maximize power, the groups were pooled. Neural measures of the posterior VLPFC were drawn from the ROI demonstrating a significant group effect (-50 8 22) and neural measures of the mid-VLPFC were drawn from the anterior-most ROI (-40 32 22) that was maximally distant from the posterior VLPFC. The latter choice minimized overlap in the activation clusters that might occur due to spatial smoothing.

Starting with the posterior-VLPFC, we tested the relationship between inhibition-related reductions in maintenance (PreCue – PostCue activation) and behavioral performance (Lure – Control error-rate). Robust regression indicated a significant negative relationship ($t(34) = -3.22, p < 0.005$; Spearman's $\varrho = -0.5753, p < 0.0005$), such that participants who appropriately inhibited irrelevant items from WM showed reduced

behavioral errors. Next, we examined the relationship between interference-control related activations in the mid-VLPFC (Lure – Control activation) and behavioral performance. Robust regression indicated a significant positive relationship ($t(34) = 2.88$, $p < 0.01$; Spearman's $\varrho = 0.4135$, $p < 0.05$): participants that demonstrated the greatest difficulty with the Lure probes behaviorally also demonstrated the greatest interference-control related activations in the mid-VLPFC. Finally, we examined the relationship between inhibition, as indexed by PostCue reductions in maintenance-related activation in the posterior VLPFC, and interference-control, as indexed by Lure > Control activations in the mid-VLPFC. Robust regression indicated a significant negative relationship ($t(34) = -3.04$, $p < 0.005$; Spearman's $\varrho = -0.4829$, $p < 0.005$). Repeating the above analyses with a co-variate for group led to similar results (posterior-VLPFC and behavior: $t(33) = -2.34$, $p < 0.05$; mid-VLPFC and behavior: $t(33) = 1.87$, $p = 0.07$; posterior-VLPFC and mid-VLPFC: $t(33) = -2.48$, $p < 0.05$). Together, these results indicate a strong inter-relationship between the posterior VLPFC, mid-VLPFC, and behavioral performance.

Thus far we have speculated that impaired inhibitory control over WM in PSZ leads to increased reliance on interference-control at the probe and subsequent behavioral impairments. Such an account predicts that inhibitory control over WM mediates the relationship between activations in the mid-VLPFC related to interference-control and behavioral interference. To examine this possibility, we performed mediation analysis using the mediation toolbox implemented in SPM (Wager, Davidson, Hughes, Lindquist & Ochsner, 2008; Wager, Waugh, Lindquist, Noll, Fredrickson & Taylor, 2009) including the PreCue – PostCue contrast in posterior VLPFC (inhibition), the Lure – Control

contrast in mid-VLPFC (interference-control), and the Lure – Control difference in error-rate (behavioral performance). Paths were estimated with robust regression and significance was assessed using a permutation test with 10,000 samples.

Confirming the centrality of inhibitory control over WM, a significant mediation effect was found ($z = 2.08$, $p < 0.05$; Figure 8). When accounting for the mediating effect of inhibitory control over WM, the relationship between interference-control in the mid-VLPFC and behavioral performance was no longer significant ($z = 1.30$, $p > 0.15$).

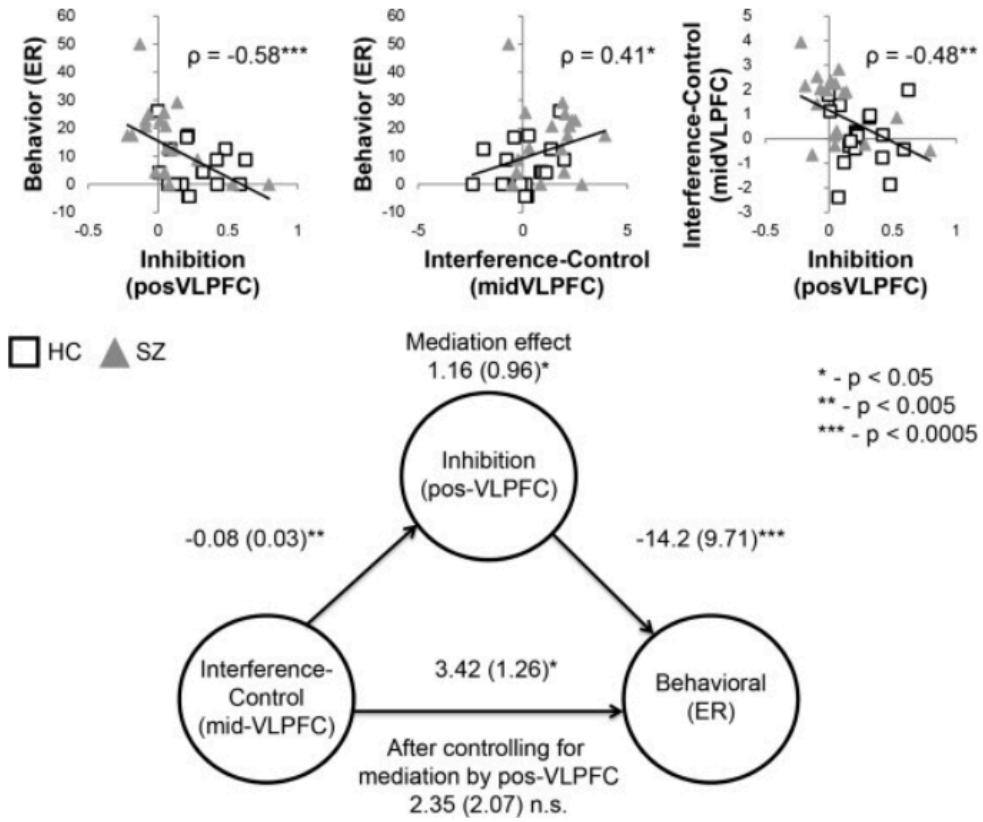


Figure 8. Correlations and mediation analysis. Top: correlations between measures of interest. Behavioral performance reflects the behavioral difference in error-rate between Lure and Control

All other paths were significant (all $z > 2.40$, $p < 0.05$). To determine the selectivity of this effect, we calculated an alternative model using the interference-control related activations in the mid-VLPFC as a mediator between the posterior VLPFC (inhibitory control) and behavioral performance. In this model, the mediation effect was not significant ($z = 0.61$, $p > 0.5$).

For completeness, we calculated all other possible models by fully rotating all measures. No other significant mediation effects were found (Table 5). Hence, the hypothesized model – inhibition mediates the relationship between interference-control and behavior – was the only model that yielded significant results.

X-M-Y		a	b	c'	c	ab
midVLPFC-posVLPFC-ER	**paths (s.e.)**	**-0.08 (0.03)**	**-14.2 (9.71)**	**2.35 (2.07)**	**3.42 (1.26)**	**1.16 (0.96)**
	z	**-3.03****	**-3.81*****	**1.22**	**2.40***	**2.08***
ER-posVLPFC-midVLPFC	paths (s.e.)	-0.01 (0.00)	-2.42 (1.54)	0.02 (0.04)	0.06 (0.03)	0.03 (0.02)
	z	-3.57***	-1.64	0.33	1.51	1.74†
ER-midVLPFC-posVLPFC	paths (s.e.)	0.06 (0.03)	-0.06 (0.03)	-0.01 (0.00)	-0.01 (0.00)	-0.00 (0.00)
	z	1.54	-2.19*	-1.95†	-3.57***	-1.23
midVLPFC-ER-posVLPFC	paths (s.e.)	3.53 (1.25)	-0.01 (0.00)	-0.06 (0.03)	-0.08 (0.03)	-0.03 (0.01)
	z	2.38*	-1.94†	-2.17*	-2.89**	-1.73†
posVLPFC-ER-midVLPFC	paths (s.e.)	-23.3 (6.20)	0.02 (0.04)	-2.42 (1.55)	-2.81 (1.15)	-0.41 (0.90)
	z	-3.21**	0.3	-1.67†	-2.80*	-0.61
posVLPFC-midVLPFC-ER	paths (s.e.)	-2.81 (1.15)	2.35 (2.09)	-14.2 (9.80)	-23.33 (6.22)	-6.59 (6.53)
	z	-2.78*	1.2	-3.89***	-3.13**	-0.45

Results from mediation analysis from all 6 possible models of mid-ventrolateral prefrontal cortex (midVLPFC), posterior ventrolateral prefrontal cortex (posVLPFC), and error-rate (ER) interactions. The hypothesized model is in bold. X-M-Y denotes the relationship between the predictor (X), mediator (M), and outcome (Y). † - $p < 0.1$; * - $p < 0.05$; ** - $p < 0.005$; *** - $p < 0.0005$.

Table 5. Mediation Results

Taken together, these results provide strong evidence that control over WM is the crux that links interference-control and behavioral WM impairments in SZ.

Examining Potential Motion Confounds

Recent data have indicated that differences in between-group motion can at times lead to spurious results (Van Dijk, Sabuncu, Buckner, 2012; Satterthwaite , Wolf,

Loughead, Ruparel, Elliott, Hakonarson, *et al.,* 2012; Satterthwaite, Elliott, Gerraty, Ruparel, Loughead, Calkins, *et al,* 2013). While these matters have been most directly addressed during resting state paradigms, motion may nevertheless confound task-based settings as well. Because no participant demonstrated more than a voxel of total displacement or 0.5 mm/degrees of inter-scan motion, we did not regress out motion explicitly in the analyses described in the main text. To more fully explore whether motion could have confounded our results, we calculated mean motion, maximum motion, mean rotation, and number of movements through methods described in van Djik et al., 2012. PSZ and HC did not significantly differ under any of these metrics (all $p > 0.1$), although there was a numerical trend for increased mean motion in PSZ (0.059 mm) compared to HCs (0.045 mm; $t(34) = 1.60$, $p = 0.12$).

To ensure that the non-significant motion differences could not account for our results, we included 24 motion regressors to capture linear, quadatric, differential, and quadratic differential motion (Satterthwaite, Elliott, Gerraty, Ruparel, Loughead, Calkins, *et al* , 2013, Lund, Nørgaard, Rostrup, Rowe & Paulson, 2005). Inclusion of these regressors did not qualitatively alter the results. Both the critical group difference in the PreCue > PostCue contrast in the left posterior-VLPFC ($t(34) = 2.32$, $p < 0.05$) and Lure > Control contrast in left mid-VLPFC ($t(34) = 2.32$, $p < 0.05$) remained significant. Hence, it does not appear that motion confounded the present results.

Ruling out General WM Deficits

We previously found that PSZ could appropriately inhibit distractors prior to entry into WM, thereby ruling out an encoding or general maintenance deficit in WM (Smith,

Eich, Cebenoyan & Malapani, 2011). However, PSZ demonstrated increased error-rates relative to HC even to Control probes in the present study. To examine whether the described patterns could be explained by a general WM deficit, we sub-sampled the patient group by excluding four participants demonstrating less than 90% accuracy on Control probes. Performance in the sub-sampled patient group (sPSZ) was thus equated with that of HCs for Control probes (99.5% vs. 98.8%, $t(30) = 0.8$, $p > 0.4$). Nevertheless, sPSZs still demonstrated impaired performance on Lure probes relative to HC ($t(30) = 2.46$, $p < 0.05$) and the group difference in Lure compared to Control probes remained ($t(30) = 2.34$, $p < 0.05$). Critically, group differences in the PreCue > PostCue contrast in posterior-VLPFC ($t(30) = 2.09$, $p < 0.05$) and Lure > Control contrast in mid-VLPFC ($t(30) = 3.45$, $p < 0.005$) remained. As a result, these patterns are unlikely to be due to a general WM deficit.

To further examine a potential general WM deficit, we examined activations in the posterior-VLPFC during Encoding and PreCue maintenance relative to a passive baseline. Deficient general WM processes would be expected to be reflected in reduced activation in PSZ relative to HCs. This pattern was not confirmed during either Encoding ($t(34) = 0.09$, $p > 0.9$) or PreCue ($t(34) = 0.82$, $p > 0.4$). Hence, our data suggest that patient deficits are largely restricted to the PostCue phase and beyond, resulting from deficient inhibitory processes.

Encoding and PreCue Maintenance

The task was specifically designed to assess inhibition through the contrast of PreCue > PostCue and interference-control through the contrast of Lure > Control.

However, previous research has documented deficient encoding and maintenance processes in PSZ (Anticevic, Repovs & Barch, 2011; Anticevic, Repovs, Corlett & Barch, 2011; Johnson, Morris, Astur, Calhoun, Mathalon, Kiehl & Pearlson, 2006; Driesen, Leung, Calhoun, Constable, Gueorguieva, Hoffman, *et al,* 2008). While our previous research with this and a related paradigm indicated intact encoding and maintenance (Smith, Eich, Cebenoyan & Malapani, 2011), it may nevertheless be instructive to investigate those phases in more detail. Due to the design, we did not have high level control conditions to contrast against Encoding and PreCue maintenance. As a result, we report here data from contrasts of these phases against a fixation baseline.

The contrast of Encoding > Baseline revealed widespread activation in visual cortices extending into the intra-parietal sulcus (IPS), as well as activations in medial and lateral frontal cortex (Figure 9/ Supplemental Table 4). Direct comparison between groups revealed that HC demonstrated increased activation in the right IPS relative to PSZ. No areas demonstrated the reverse pattern. Targeted examination of each cluster activated across groups revealed no other group differences (all $p > 0.1$).

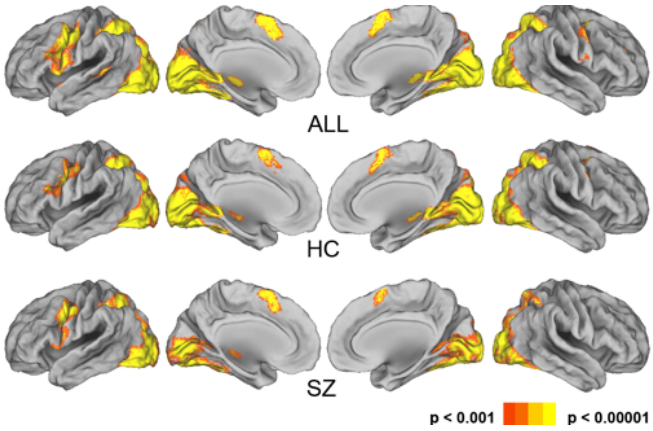


Figure 9. Contrast of Encoding - Baseline for Healthy Controls (HC) and People with Schizophrenia (SZ)

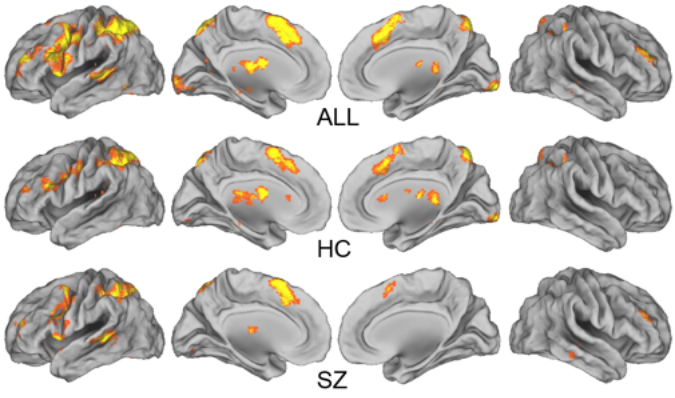


Figure 10. Contrast of PreCue - Baseline for Healthy Controls (HC) and People with Schizophrenia (SZ)

The contrast of PreCue > Baseline revealed activations in bilateral prefrontal and posterior parietal areas, as well as portions of occipital and temporal cortex (Figure 10/Supplemental Table 5). Direct comparisons between groups revealed no differences at a whole-brain corrected threshold. Targeted examination of each cluster activated across groups revealed increased activation in the right IPS for HC relative to PSZ ($t(34) = 2.44$, $p < 0.05$). No other comparison was significant (all $p > 0.15$).

Discussion

This study investigated the component processes that underlie WM deficits in SZ. Our results indicate WM impairments in SZ in three specific ways. First, PSZ demonstrated impaired inhibition of irrelevant content in WM evidenced by reduced PreCue to PostCue activation difference in the posterior VLPFC. Second, PSZ exhibited a failure to overcome familiarity-induced interference of Lure probes demonstrated by increased behavioral error-rates to Lure probes relative to Control probes. Finally, PSZ exhibited increased reliance on interference-control at the time of retrieval, evidenced by selectively increased activation to Lure probes relative to Control probes in the mid-VLPFC. These data indicate that impaired inhibitory control in WM has downstream consequences that adversely impact behavior.

Our data also indicated that PSZ made more errors on Valid probes than HC, even after controlling for performance on Control probes. This result may also stem from inappropriate inhibitory control. When irrelevant items are appropriately removed from WM, Valid probes are distinguished from Lure probes as a function of memory strength. However, if irrelevant items are not inhibited, Valid and Lure items are more difficult to distinguish. Hence, impaired inhibitory control can simultaneously lead to erroneous endorsements of Lure probes and rejections of Valid probes.

Relation to other findings

A recent review (Barch & Ceaser, 2012) suggested SZ-related deficits in a variety of cognitive domains including WM could be explained by impairments in proactive control, which allows for goal-relevant information to be activated and irrelevant information to be inhibited in anticipation of cognitive demands that require use of the information (Braver, Gray& Burgess, 2007; Bunge, Wallis, Parker, Brass, Crone, Hoshi & Sakai, 2005). The present results fit well within such a framework. While HC appropriately inhibited irrelevant items from WM in anticipation of the probe, PSZ failed to do so, consistent with impaired proactive control. The engagement of proactive control is flexible and may be useful during different phases of tasks depending on demands (Braver, Gray& Burgess, 2007). Previous research has demonstrated impairments during WM encoding and maintenance in PSZ (Anticevic, Repovs & Barch, 2011; Anticevic, Repovs, Corlett & Barch, 2011; Johnson, Morris, Astur, Calhoun, Mathalon, Kiehl & Pearlson, 2006; Driesen, Leung, Calhoun, Constable, Gueorguieva, Hoffman, et al., 2008) a pattern that contrasts with the present results. In those studies,

encoding and maintenance demands were likely increased due to the use of abstract stimuli (Anticevic, Repovs & Barch, 2011; Anticevic, Repovs, Corlett & Barch, 2011) or increased loads (Johnson, Morris, Astur, Calhoun, Mathalon, Kiehl & Pearlson, 2006; Driesen, Leung, Calhoun, Constable, Gueorguieva, Hoffman, et al., 2008). In such cases, HC may enlist proactive control processes to facilitate encoding and maintenance, whereas PSZ do not. This may take the form of chunking or re-coding strategies to ease demands on maintenance processes. Our data indicate that with verbal material and manageable load, PSZ exhibit largely intact encoding and maintenance, but are impaired in proactively inhibiting items from WM in preparation for future responding. These data suggests that PSZ have preserved basic maintenance processes, but impaired cognitive control over maintained information.

While we have focused analysis on the VLPFC due to our prior hypotheses, comprehensive analyses revealed other regions that differ between PSZ and HC during different phases of the task. Most notable, during Encoding and the PreCue maintenance interval, HC demonstrated increased recruitment of the right IPS compared to PSZ. Although the contrasts revealing these effects were unconstrained due to the use of a simple resting baseline as a control condition, it is tempting to speculate on the role of the right IPS in the present study. Previous research has demonstrated that the IPS is a central node in the dorsal attention network (Corbetta & Shulman, 2002), playing a role in top-down attention and WM (Chun, Golomb & Turk-Browne, 2011). Through interactions with visual cortices, it is thought that the IPS is involved in binding object features (Shafritz, Gore & Marois, 2002; Ptak, 2012). Here, the IPS may be important in binding word and color information. Reduced activation of the right IPS in PSZ may

reflect impaired encoding and maintenance of color-word bindings. This could, in turn, lead to impaired use of color cues to discard irrelevant information from WM. We have previously demonstrated that PSZ have no difficulties in using color cues to guide encoding in WM (Smith, Eich, Cebenoyan & Malapani, 2011). Hence, SZ deficits may be restricted to cases where bound information must be maintained in the absence of external stimulation. Examining the relationship between the binding functions of the IPS and control processes would be an interesting avenue for future research.

In addition to the left mid-VLPFC, PSZ also demonstrated increased activation in the dorsal anterior cingulate cortex and left preMotor cortex in response to Lure probes compared to Control probes. These areas are robustly activated across a variety of tasks that produce response conflict (Nee, Wager & Jonides, 2007). It is likely that PSZ's uncertainty with how to respond to Lure probes elicited response conflict. The activation of these areas may therefore be a reflection of this conflict.

Our results corroborate a growing body of research in HC that links the mid-VLPFC to resisting interference and appropriate selection of information at the time of retrieval (Ranganath, 2006, Jonides, Lewis, Nee, Lustig, Berman & Moore, 2008). The mid-VLPFC (BA 45) is thought to select goal-relevant information when multiple competing representations are active in memory (Badre & Wagner, 2005). The left mid-VLPFC has also been implicated in the resolution of proactive interference, in which memory of a past experience interferes with processing of a subsequent experience (Jonides & Nee, 2006; Jonides, Smith, Marshuetz, Koeppe & Reuter-Lorenz, 1998; Nee, Jonides & Berman, 2007; Zhang, Leung & Johnson, 2003; Badre & Wagner, 2005). A

common selection mechanism may account for both forms of control (Nee, Brown, Askren, Berman, Demiralp, Krawitz & Jonides, 2012).

Similar impairments in inhibitory control may underlie cognitive deficits in other psychiatric disorders such as depression, obsessive compulsive disorder, or attention deficit hyperactivity disorder (Harkin, Miellet & Kessler, 2012; Joormann & Gotlib, 2008; Joormann, Nee, Berman, Jonides & Gotlib, 2010; Nakao, Nakagawa, Nakatani, Nabeyama, Sanematsu, Yoshiura, et al., 2009; Schecklmann, Ehlis, Plichta, Dresler, Heine, Boreatti- Hummer A, et al., 2013). In a similar task to that used here, PSZ with depression demonstrated a specific deficit in inhibiting negatively, but not positively valenced content from WM (Joormann, Nee, Berman, Jonides & Gotlib, 2010; Berman, Nee, Casement, Kim, Deldin, Kross, et al., 2011). This deficit was hypothesized to underlie the rumination of negative information in depression. Thus, examining inhibition and its correlates is an important endeavor to pinpoint cognitive impairments in psychiatric populations in general.

Chapter 3

Schizophrenia and Emotional Rubbernecking

Orienting towards salient information can be adaptive (Anderson & Phelps, 2001; LeDoux, 1996). However, this often automatic, bottom-up process can also be in opposition to one's active cognitive goals: it would be better for people to keep their hands on the wheel and eyes on the road instead of rubbernecking. And yet it is often times impossible to not crane your neck to see the accident on the other side of the highway. In these types of situations, a lack of attention to emotionally loaded stimuli might be adaptive.

Limitations of attentional capacity have long been considered a core cognitive deficit in SZ (Bleuler, 1911/1950; Carter et al., 2010; Gjerde, 1983; Zubin, 1975). A growing body of research suggests that PSZ show deficits in the ability to use top-down processes to guide attention (Fuller, Luck, Braun, Robinson, McMahon & Gold, 2006). Hahn, Robinson, Kaiser, Harvey, Beck, Leonard, Kappenman, Luck and Gold (2010), for example, showed that when salient (flickering) distractor items were introduced during the encoding phase of a WM task, PSZ showed attentional deficits, which led to impaired memory for less salient (non-flickering) target items. When attention was guided by bottom-up, automatic processes, however, as when target items were highly salient, PSZ were able to shift attention and filter less salient distractors effectively (Gold, Fuller, Robinson, McMahon, Braun & Luck, 2006; Luck, Fuller, Braun, Robinson, Summerfelt & Gold, 2006). Based on this, it stands to reason that PSZ might show impaired

performance relative to HC in a task in which emotionally salient information must be ignored.

Emotionally valenced information draws attention to a greater extent than does neutral information in HC (Bradley, 2009; Hajcak, MacNamara & Olvet, 2010; Ohman, Flykt & Esteves, 2001; Egeth & Yantis, 1997). PSZ, though, show deficits in the processing of and attention to emotional information (Edwards, Jackson & Pattison, 2002a,b; Gur et al., 2002; Loughland, Williams & Gordon, 2002). A recent meta-analysis of studies from 1970-2007 assessing emotion recognition and differentiation in PSZ across a wide range of tasks revealed that PSZ showed marked deficits in the perception of emotional faces, including the recognition of negatively and positively valenced faces. They also showed deficits in the ability to differentiate between emotions of different intensities (Kohler, Walker, Martin, Healey & Moberg, 2010). It follows that the compelling attention-drawing effects of emotional stimuli as compared to neutral stimuli may be smaller for PSZ than for HC for this reason. Thus, PSZ might do better than HC in a task in which emotionally salient information must be ignored.

In a previous study (see Chapter 1), we found that PSZ's performance was equal to that of HC on a cognitive task in which irrelevant perceptual information had to be ignored at the time of encoding, before items had entered WM, even though PSZ were impaired when they were required to suppress the same information once it had entered WM (Smith et al., 2011). In that study, PSZ and HC were given an instruction to remember either the red or blue words. In the Ignore task, the instruction cue came before a set of red and blue words. In the Suppress task, the instruction cue came after

the presentation of the colored words. Finally, a test probe was given. The test probe required a positive response if it was one of the words that corresponded to the instruction cue's color. It required a negative response if it was one of the words of the other color, or if it was a new, unpresented word. While there were differences in performance when the PSZ had to suppress information that had already entered WM, our results showed that PSZ performed equivalently to HC when they had to ignore irrelevant perceptual information, indicating that they did not have deficits in the ability to selectively attend to relevant perceptual information and ignore irrelevant perceptual information that had not yet entered WM.

In Smith, Eich, et al. (2011), we used neutral words and a word-cue instructing participants to attend to either the red or blue words. Here, though, we used emotional stimuli (Happy, Fearful and Neutral faces) and an arrow-cue instructing participants to attend to the left or right (see Figure 11). Thus, the valences of the face-stimuli were incidental to the task requirements. In HC, the presentation of irrelevant but emotional information hurts performance on an unrelated primary task. For example, emotional distractors presented during the WM maintenance phase (the delay interval between presentation of the to-be-remembered information and the test probe) impairs performance (Dolcos, Diaz-Granados, Wang, & McCarthy, 2008). Similarly, Anticevic, Repovs, Corlett and Barch (2011) investigated these effects in PSZ and found that their performance at retrieval was compromised by distracting emotional items introduced during the WM maintenance phase. No study to date, however, has investigated how PSZ would perform on a task in which irrelevant emotional information competed with goal-relevant information at the time of encoding, before information entered WM.

On the one hand, PSZ might perform worse than HC in a task in which emotional information competes with task-relevant information as they did in Anticevic et al.'s (2011) study: they might not be able to use top-down processes to selectively encode only the relevant information because attention is drawn towards the salient emotional stimuli through bottom-up processes, which would result in impaired performance on the task. A finding such as this would be in line with previous studies showing top-down attentional deficits. On the other hand, it is our hypothesis that in this situation, PSZ might actually benefit from emotional processing deficits. The emotional information might not be seen as salient to PSZ, and therefore they might not attend to or encode this information. This would result in better performance relative to HC, who are likely to attend to these stimuli because of their salience. The current study aimed to investigate this question.

Methods

Participants

Participants included 25 HC and 22 PSZ. Data from one additional person with SZ was excluded because s/he did not respond to over 20% of experimental trials. The remaining participants were comparable in non-response rates on the task (PSZ averaged 5.05 (standard deviation=6.1), while HC averaged 4.6 (standard deviation=5.5); this difference was not significant ($t(33)=0.23$). The demographics of the two groups are shown in Table 6, along with clinical ratings and chlorpromazine equivalents (American Psychiatric Association, 1997; Woods, 2003) for the PSZ. There were no significant differences between PSZ and HC in age ($t(45)=.41$), number of years of education

(t(45)=1.5), or gender (t(45)=.09). HC, recruited through local and online advertisements, reported being free of current or past psychiatric or neurological illness, alcohol or substance dependency in the last six months, and had not used psychotropic medication, such as antipsychotics or antidepressants, in the last year. PSZ were stabilized outpeople, recruited through the Lieber Center for Schizophrenia Research and Treatment of NYSPI. All PSZ met DSM-IV criteria for SZ or schizoaffective disorder (First, Spitzer, Gibbon & Williams, 2007). Diagnoses were determined through a diagnostic conference that included information from either the DIGS (Nurnberger, Blehar, Kaufmann, York-Cooler, Simpson et al, 1994) or the Structured Clinical Interview for DSM-IV (SCID) (First & Pincus, 2002). In addition, the SAPS and SANS (Andreasen & Olsen, 1982), and the Hamilton Depression Scale (Hamilton, 1960) were used to evaluate symptom severity. Ratings for PSZ were obtained on the day of testing. All PSZ were being treated with atypical antipsychotic medication for at least three months, and had taken the

	PSZ	HC
Variable		
N	*22*	*25*
Age (in years)	39.6 (8.2)	40.6 (8.5)
Gender (M/F)	10/12	14/11
Handedness		
Right	15	22
Left	5	2
Ambidextrous	0	1
Education (in years)	15.2 (1.9)	14.4 (1.4)
Mother's Education	13.7 (4.4)	13.6 (2.1)
Father's Education	14.9 (4.4)	13.9 (3.0)
Age of Onset	25.2 (8.4)	
CPZ Equivalent	305.2 (381.7)	
SANS		
Affective Flattening/5	5.4 (8.8)	
Alogia/5	1.9 (2.5)	
Avolition/Apathy/5	7.38 (4.7)	
Asociality/ Anhedonia/5	7 (6.7)	
Global	5.25 (4.0)	
Total	17.05 (14.5)	
SAPS		
Hallucinations	6.26 (8.6)	
Delusions	3.1 (5.5)	
Bizarre behavior	0.53 (1.9)	
Thought Disorder	2.3 (4.2)	
Global	2.84 (3.3)	
Total	10.77 (14.7)	
Hamilton Depression	2.85 (3.3)	

Table 6: Demographics and clinical ratings of Healthy Controls (HC) and People with Schizophrenia (PSZ)

same type and dose of medication for at least one month before the day of testing. All participants were English-speaking.

After the procedure was fully explained to participants, written informed consent was obtained. Capacity to participate in the experiment was also assessed for each person with SZ via an interview process with a psychiatrist not related to the study. The research protocol was approved by the Institutional Review Board of the NYSPI and Columbia University.

Procedure

The task is illustrated in Figure 11. PSZ and HC completed a novel, emotional version of the Ignore task (modeled upon Smith, Eich et al.'s (2011, Study 1), and Nee & Jonides' (2008, 2009) tasks). An arrow pointing either to the left or right (instruction cue) was followed by the presentation of two faces (memory set). The direction of the arrow was counterbalanced across the experimental trials, and indicated which face the participant should remember: the one on the left side of the screen or the one on the right side of the screen. Trials contained either only male or only female faces. The faces were presented in 6 combinations, each of which contained an emotional component, although the valence of the face was incidental to the task from the perspective of the participant (they were only instructed to attend left or right): Attend Happy, Ignore Fear (illustrated in Figure 11); Attend Happy, Ignore Neutral; Attend Neutral, Ignore Fear; Attend Neutral, Ignore Happy; Attend Fear, Ignore Neutral; Attend Fear, Ignore Happy. The position of the type of emotion was counterbalanced across the experiment. The presentation of the two faces—one of which was to be remembered and one of which was

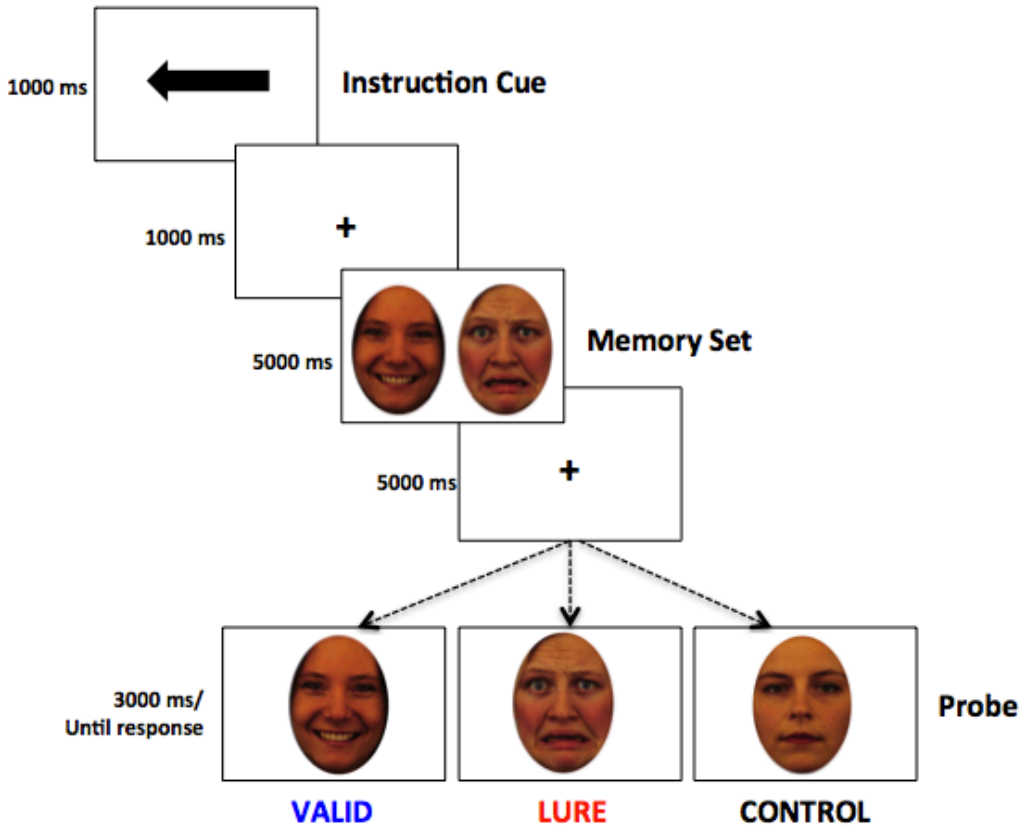


Figure 11. Emotional Ignore Task Schematic (illustrating an Attend Happy, Ignore Fear trial)

to be ignored according to the arrow's direction--was followed a delay period, during which time participant should have retained the cued-face in memory. Lastly, a single test probe face appeared in the center of the screen. The probe required a positive response, made by pressing the "1" key on the keyboard, if it matched the face that the arrow had pointed to (Valid). It required a negative response, made by pressing the "0" key on the keyboard, if it was either the face that the arrow had not pointed to (Lure), or if it was a new face (Control). Control probes, which were always new neutral faces, were included in the design as a baseline for performance, as they were expected to show low false alarm rates. Participants completed 6 blocks of the task. Each block consisted of 6 Valid probe trials, 4 Lure probe trials and 4 Control probe trials. The experimental

task was presented using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA).

Materials

The stimuli consisted of 96 pictures of faces from the Karolinska Directed Emotional Faces set (Lundqvist, Flykt & Öhman, 1998). Thirty-two faces (half male, half female) were chosen for each emotion category, Happy, Fearful and Neutral. Faces were masked with an oval.

Results

The main data of interest were the discriminability index (*d'*), Hit Rates (correctly saying yes on Valid trials), and False Alarm Rates (incorrectly saying yes on Lure or Control trials) for HC and PSZ. We began by investigating *d'*, which provides an overall index of performance on the task. As is illustrated in Table 7, the PSZ had significantly higher *d'*s than did HC, indicating that they performed better on the task overall (t(45)=2.16, *p*=.04).

Variable (Mean (SD))			
	Hit Rate	False Alarm Rate	*d* Prime
HC	0.87 (.16)	0.13 (.13)	2.73 (1.14)
PSZ	0.93 (.08)	0.06 (.06)	3.35 (.77)

Table 7. Performance on the Emotional Ignore task as measured by *d'*, Hit Rate and False Alarm rate for Healthy Controls (HC) and People with Schizophrenia (PSZ)

To determine whether PSZ did better on the task because they said yes on Valid trials more than did HC, or because HC false alarmed on Lure or Control trials more than did PSZ, we separately examined Hit Rates and False Alarm Rates, as independent

factors. A Group (HC vs. PSZ) by Index (Hit Rates vs. False Alarm Rate) ANOVA revealed a significant interaction ($F(1,45)=3.96$, $p=.05$). There was no difference in Hit Rate between Groups. However, PSZ had a lower False Alarm Rates than did HC. Post-hoc t-tests confirmed that Hit Rate did not differ by Group ($t(45)=1.39$, *ns*). Both PSZ and HC exhibited high Hit Rates. However, PSZ had a significantly lower False Alarm Rates than did HC ($t(45)=2.28$, $p=.03$). The main effect of Hit Rate versus False Alarm Rate was significant, of course ($F(1,45)=686.11$, $p=.000$), and the Group main effect was not significant ($F(1,45)<1$).

We next performed an ANOVA of the relationship between Group, False Alarm Rates for Lure versus Control Probes Types, and the 6 Emotional Conditions, which is illustrated in Figure 12.

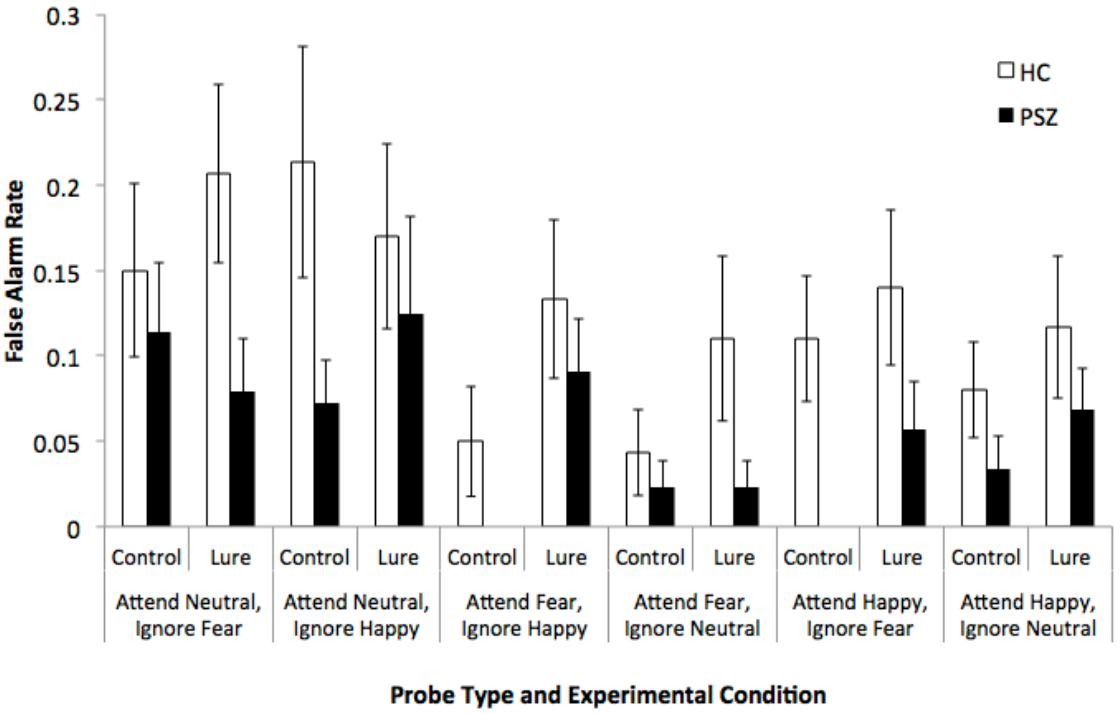


Figure 12: False Alarm Rates on trials that required a negative response (Lure and Control trials) for People with Schizophrenia (PSZ) and Healthy Controls (HC) by Emotional Condition. Note that in the task, participants attended to one face by virtue of an arrow-cue, not a word-cue. The valence of the face was incidental to the task requirements, and Emotional Condition was not made explicit to participants.

The ANOVA revealed a significant effect of Group ($F(1, 45)=4.91, p=.03$). PSZ made fewer false alarms than did HC across all Emotional Condition types. The main effect of Emotional Condition was also significant ($F(1, 45)=6.29, p<.001$). Pairwise Bonferonni contrasts revealed that more false alarms were made in the Attend Neutral, Ignore Fear condition than in the Attend Fear, Ignore Neutral condition ($p=.02$), and in the Attend Neutral, Ignore Happy condition than in the Attend Fear, Ignore Neutral condition ($p=.01$). Neither the main effect of Probe Type (Lure vs. Control), nor any of the interactions were significant.

Consistent with the design of the experiment, we were interested in investigating whether HC demonstrated a pattern of results that would fit with previous research showing impaired attentional control when the distracting, to-be-ignored information was emotional as opposed to neutral (Perlstein, Elbert & Stenger, 2002). Accordingly, as is illustrated in Figure 13, we collapsed across the valence of emotional stimuli (Happy and Fearful) and compared performance on the Lure trials when the target was emotional and the distractor was neutral to when the

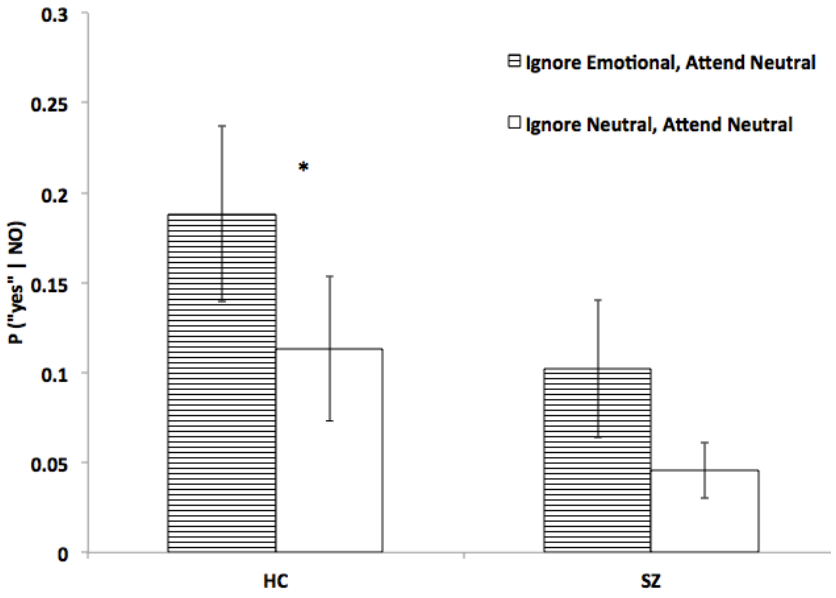


Figure 13. False Alarm Rates for Healthy Controls (HC) and People with Schizophrenia (PSZ) on Emotional and Neutral Trials

target was neutral and the distractor was emotional. Indeed, a paired *t*-test revealed that HC said yes in error significantly more when they were to attend to a neutral face and ignore an emotional face than when they were to attend to an emotional face and ignore a neutral face ($t(24)=2.59$, $p=.02$), suggesting that emotional information that should have been ignored was instead encoded by HC. The same analysis conducted for PSZ was not significant ($t(21)=1.9$, *ns)*, suggesting that they did not encode the irrelevant, but emotional information.

We further investigated the relationship between performance (*d*', Hit Rate and False Alarm Rate) and clinical symptoms (see Table 6) in PSZ. No correlations between performance and clinical symptoms were significant.

Finally, we investigated reaction times (RT) for PSZ and HC. A generalized deficit in schizophrenia would predict slower RTs for PSZ than for HC. As expected, there was a main effect of Group such that PSZ were slower than HC overall (1332ms vs. 1136ms respectively, ($F(1, 45)=4.92$, $p=.03$)). The main effect of Probe Type was also significant ($F(2, 90)=5.43$, $p=.006$). Post-hoc Bonferonni tests revealed that Lure probes produced significantly longer RTs than Valid probes overall (1265ms vs. 1195ms respectively, $p=.014$). The interaction between Probe Type and Group was not significant ($F(1,45)<1$).

In summary, these results indicate that the locus of the benefit shown by the PSZ was that they said yes *in error* to the Lure items (the to-be-ignored distractors) and to unpresented Control items *less* frequently than did HC.

Discussion

A number of studies have investigated attentional control, the effects of salient distractors on the maintenance of information in WM, and emotional recognition in PSZ as independent factors, yet few have investigated these processes in conjunction. In the current study, PSZ and HC completed a novel task in which they were instructed to attend to one face and ignore another based on the direction of an instruction cue arrow. The emotional valence of the two presented faces was manipulated in such a way that sometimes the face that the participant should have ignored was neutral and the target was emotional, whereas other times the distractor was emotional (and the target item was either emotional or neutral).

In a previous study, we found that neither HC nor PSZ had difficulty ignoring neutral material before it had entered WM. According to past literature, however, HC, have difficulty ignoring emotional materials. In the current study, we predicted that PSZ would perform better than HC due to the very affective processing deficits that are central to their symptomatology. Consistent with our hypothesis, PSZs outperformed HC. They had Hit Rates equivalent to (and in fact numerically higher than) HCs, and their *d'*s were higher than HC. Most noteworthy, they outperformed HC by making fewer false alarms. Given that PSZ generally show deficits in cognitive tasks (Chapman & Chapman, 1973), and that impairments in WM are thought to be a hallmark cognitive deficit in the disease (Goldman-Rakic, 1994), these results are surprising.

Affect Labeling

Research in HC suggests that affect labeling (the explicit verbal articulation of emotion) diminishes emotional reactivity (see Lieberman, Eisenberger, Crockett, Tom, Pfeifer & Way, 2007). In our task, emotion was attended to incidentally. An arrow instructed participants to attend to and remember the face on the left or the right side of the screen, which could be either an emotional or a neutral face. The emotional component of the task was therefore never made explicit to the participants. However, in every trial, emotional information was present: when a participant was to attend to a neutral face, the distractor face was an emotional face, and when the distractor face was neutral, the target face was emotional. Because of this, emotional information may have been particularly salient to HC, regardless of Emotional Condition. PSZ, who show deficits in the processing of emotion (Kohler et al., 2010), may have derived a benefit to performance due to emotional processing deficits; just as they performed on par with HC in our previous study in which neutral words were used, in the current study, the introduction of emotionally valenced stimuli did not lead to impairments in attentional control at encoding.

The Amygdala and Affective Processing

The amygdala is thought to play a key role in affective processing (see LeDoux, 2000). A study by Gur et al., (2002) found under-recruitment of the left amygdala in PSZ during a valence discrimination task in which participants had to distinguish positive from negative facial expressions. This under recruitment was hypothesized as an explanation for typical emotion processing deficits seen in PSZ. A more recent meta-

analysis by Anticevic, Van Snellenberg, Cohen, Repovs, Dowd and Barch (2012) investigated amygdala activation in PSZ during tasks that used emotionally evocative stimuli, including faces and IAPS. Results of this study showed only small differences in amygdala activation when PSZ were compared directly to HC, in contrast to the findings of Gur et al., (2002). However, amygdala under-recruitment was reported for tasks in which neutral information was contrasted with emotional information. It is possible that the superior performance of PSZ in our task may be tied to this finding. HC, but not PSZ, made mistakes significantly more often when they were supposed to attend to a neutral face and ignore an emotional face as compared to compared to when they needed to attend to an emotional face and ignore a neutral face. One explanation for this pattern is that PSZ may not orient towards emotional information in the same way as HC because they are exhibiting dysfunctional amygdala activity due to the simultaneous presentation of both emotional and non-emotional stimuli. If PSZ are not drawn to or distracted by emotionally salient information in the task, they may be able to focus attention on the goal-relevant, to-be-remembered stimuli and ignore all other information, even emotional information. The lack of automatic orienting to such information might result in fewer false alarms to information that should not have been attended to in the first place, according to the task requirements.

Limitations

First, RT differences might have had an effect on our results. We found that PSZ reacted more slowly than did HC overall, which suggests that their superior performance could be attributed to a speed-accuracy tradeoff. However, if this were the case, an

interaction between Group and Probe Type would be expected, such that PSZ would be particularly slow in conditions in which their performance was especially good. However, the interaction between Probe Type and Group was not significant. Second, the data suggest that PSZ might be reacting to emotional stimuli as if they were neutral stimuli. A follow up study containing a Neutral-Neutral versus an Emotional-Neutral condition could help to determine whether or not this is the case. PSZ would be expected to perform equivalently to HCs on the Neutral-Neutral condition (as they did in our previous study which contained only neutral words, see Smith et al., 2011). However, in the Emotional-Neutral condition we would expect results similar to the present results, such that PSZ would perform better than HC. Finally, follow-up, using a larger sample size, an increased number of experimental trials, and brain imaging to investigate amygdala activity during the task, would help to determine the precise nature of PSZ superior performance.

Conclusions

Although deficits in cognitive control in SZ have been extensively studied, a number of questions still remain. The preecding studies aimed to address two key, as of yet unresolved, issues. The first question probed whether cognitive control is impaired globally, or if instead only certain components of cognitive control are impaired in SZ. To answer this question, Chapter 1 presents data from a comparison of PSZ and HC in their abilities to both ignore distracting perceptual information prior to entry into WM, and inhibit distracting information once it had entered WM. In the "Ignore" task, which fostered perceptual selection, participants saw a cue to remember either red or blue words, followed by a memory- set (2 red, 2 blue), a brief delay, and then a probe. In the "Suppress" task, the memory-set came before the instruction-cue, and hence selection had to occur in WM. RT and percentage errors for positive probes ("Valid"), and two kinds of negative probes, those that were supposed to have been dropped from WM ("Lures") and those that had not appeared in the memory-set ("Controls") were recorded.

The data presented in Chapter 1 indicated that PSZ can control what information gets into mind. In the Ignore Task, they used cognitive control as effectively as HC to filter information on a perceptual level, prior to entry into WM. However, PSZ had difficulty filtering unwanted information out of mind. In the Suppress Task, the cognitive control over information already in WM was found to be impaired. This dissociation implies that there are (at least) two different selection mechanisms, suggesting that PSZ have a specific, not a global, cognitive control deficit.

Chapter 2 aimed to determine from which component processes of the WM stream the behavioral impairment in the Suppress task stemmed. fMRI was used as PSZ and HC performed a version of the Suppress task that was optimized to allow for separate neural assessments of 1) WM maintenance, 2) inhibition, and 3) interference-control in response to recognition probes. Before inhibitory demands, posterior VLPFC, an area involved in WM maintenance, was activated to a similar degree in both HC and PSZ, indicating preserved maintenance operations in SZ. When cued to inhibit items from WM, HC showed reduced activation in posterior VLPFC, commensurate with appropriately inhibiting items from WM. However, these inhibition-related reductions were absent in PSZ. When later probed with items that should have been inhibited, PSZ showed reduced behavioral performance and increased activation in mid-VLPFC, an area implicated in interference control. A mediation analysis indicated that impaired inhibition led to increased reliance on interference control and reduced behavioral performance. In SZ, impaired control over memory, manifested through proactive inhibitory deficits, leads to increased reliance on reactive interference-control processes. The strain on interference-control process results in reduced behavioral performance. Thus, inhibitory deficits in SZ may underlie widespread impairments in WM and cognition.

Although the Suppress task was optimized to be able to identify specific points at which breakdowns in cognitive control that lead to behavioral deficits might have occured, it is interesting to speculate about processes occuring at other points of the task. For example, during the encoding (word-set) phase of the task, a group level comparison revealed reduced activation of the right IPS in PSZ. The IPS has been shown to play a role in top-down attention and WM (a central node in the dorsal attention network), and

is involved in binding object features. Here, it may be implicated in binding word and color information. Thus, dysregulation at the time of encoding (a failure to bind color-word pairs) could lead to impaired use of color cues to discard irrelevant information from WM at the time of the instruction cue, thus resulting in behavioral deficits. Future work could examine this possibility. Further, I have used the term "inhibition" throughout to index a difference in maintenance of items pre and post remember cue. However, developing a task optimized to investigate neural activity at the time of the remember cue, for example one in which the remember cue is presented on some trials and not presented on other trials, would allow for more direct evidence of inhibition or suppression or updating of WM contents in memory, and would help to underlie the exact mechanistic differences occurring between the HC and PSZ.

The second question posed was, given that PSZ were able to effectively ignore distracting information prior to entry into WM, as was described in Chapter 1, does the nature of the information affect cognitive control? To answer this question, HC and PSZ were compared in their ability to ignore emotionally salient perceptual information prior to entry into WM. Results indicated that hit rates were equal for HC and PSZ, but that the PSZ made fewer false alarms—resulting in overall better performance-- than the HC. Deficits in emotional processing in PSZ appear to provide an advantage to them in situations in which salient, emotional information competes with active cognitive goals.

The results presented here indicate that PSZ are intact at ignoring multiple types of information prior to entry into WM: They are equivalent to HC for neutral words, as is shown in Chapter 1. They are better than HC for emotional faces, as is evidenced in

Chapter 3. However, PSZ have specific cognitive control deficits, including in the ability to inhibit information that is already in WM, described in Chapter 2. These findings raise a number of intreesting questions that could be explored in the future, and provide further insights into cognitive control deficits in SZ. Can we apply the findings from these studies to enhance training and rehabilitation in people with schizophrenia? Can we use this knowledge to help predict onset (in adolescents at risk or people in the prodromal phase)? Follow up to test the effects of saliency (using emotional faces) on inhibitory processes for information already in mind would help dissociate further the internal-external distinction in cognitive control deficits found in this research. The use of eye-tracking would help to determine the locus of PSZ superior performance in the Emotional Ignore task, described in Chapter 3. Does it derive from a difference in low-level visual processing (e.g., are PSZ not looking at the Lure faces)? Similarily, PSZ do not activate regions important for the determination of emotional salience, including the amygdala, ventral striatum, ACC and medial prefrontal cortex, an area known to mediate interactions between cognition and emotion (Ochsner & Gross, 2005). Thus, the use of fMRI would also be informative in uncovering the nature of the benefit exhibited by PSZ in Chapter 3.

Supplemental Tables

	Region	Area	X	Y	Z	VOX	Peak Z
All Participants	left IFG - oper	44	-52	10		317	4.38
	left IFG - oper	44	-54	8	16		4.16
	left IFG - oper	44	-50	8	22		3.96
	left IFG - oper	44	-52	16	22		3.8
	left IFG - oper	44	-50	12	28		3.72
	left fusiform	37	-50	-66	-18	1647	6.36
	left IPS	7	-28	-62	44	5833	5.73
	right cerebellum		24	-64	-22	1708	5.64
	left STG	22	-62	-42	8	523	5.48
	left preMotor	6	-48	2	58	2239	5.43
	left preSMA	6	-2	4	62	192	4.87
	right ant DLPFC	46	40	50	24	133	4.19
HC Only	left IFG - oper	44	-48	8	20	1055	4.91
	left fusiform	37	-50	-66	-18	1577	5.79
	right fusiform	37	52	-62	-16	1529	5.57
	left MTG	21	-52	-48	12	428	5.43
	right IPS	7	32	-70	48	935	5.23
	left IPS	7	-24	-72	54	1230	4.82
	right PHG	30	14	-44	-2	414	4.57
	left lingual gyrus	18	-16	-92	-2	233	4.46
	left cuneus	19	-2	-92	36	1129	4.35
	left preCuneus	7	-4	-56	48	129	3.91
	right IFJ	6,44	48	8	34	99	3.86
PSZ Only	left preMotor	6	-48	2	58	794	5.43
	left IPS	7	-28	-62	44	533	4.9
	left fusiform	37	-50	-68	-18	291	4.54
	right cerebellum		24	-60	-22	138	4.44
	right SOG	19	30	-78	38	81	4.09
HC > PSZ	none						
PSZ > HC	left temporal pole	38	-42	8	-22	183	4.5
	left ACC	32	-18	46	12	165	4.15

Coordinates of peak activation are reported in MNI space. Multiple sub-peaks are reported for the posterior ventrolateral prefrontal cortex since it was a site of *a priori* interest. Abbreviations: ACC – anterior cingulate cortex; ant – anterior; IFG – inferior frontal gyrus; IFJ – inferior frontal junction; IPS – intraparietal sulcus; MFG – middle frontal gyrus; oper – pars opercularis; SMA – supplementary motor area; SOG – superior occipital gyrus; STG – superior temporal gyrus.

Supplemental Table 1. Whole-Brain Results: PreCue-PostCue

	Region	Area	X	Y	Z	VOX	Peak Z
All Participants	left IFG - tria	45	-48	24	22	228	3.96
	left IFG - tria	45	-40	32	22		3.41
	left IFG - tria	45	-38	16	22		3.33
	left calcarine	17	-18	-68	8	517	4.89
	right dACC/preSMA	32, 6	6	24	44	358	4.69
	left IPS	40	-40	-42	40	447	4.69
	left preMotor	6	-32	-4	36	402	4.65
	right preCuneus	7	8	-66	44	98	4.17
	right thalamus		12	-6	8	74	3.96
HC Only	left thalamus		-6	-20	8	435	4.82
	left preCuneus	7	-2	-62	40	343	4.67
	right calcarine	17	14	-68	6	146	4.28
PSZ Only	left IFG - tria	45	-48	20	20	198	4.28
	left IPS	40	-42	-44	38	83	4.6
	left preMotor	6	-32	-4	36	217	4.57
	left dACC/preSMA	32,6	-8	16	50	275	4.57
	left IFG - orb	47	-46	18	-4	83	4.11
	left lingual gyrus	18	-22	-68	-8	75	3.78
HC > PSZ	left thalamus		-4	-12	14	139	3.82
PSZ > HC	none						

Coordinates of peak activation are reported in MNI space. Multiple sub-peaks are reported for the mid-ventrolateral prefrontal cortex since it was a site of *a priori* interest. Abbreviations: dACC – dorsal anterior cingulate corte; IFG – inferior frontal gyrus; IPS – intraparietal sulcus; orb – pars orbitalis; SMA – supplementary motor area; tria – pars triangularis.

Supplemental Table 2. Whole-Brain Results: Lure-Control

PreCue-PostCue				
Region	**Peak**	**HC**	**PSZ**	**HC vs PSZ**
left fusiform	-134	6.31***	4.45***	1.52
left IPS	-28 -62 44	7.77***	6.18***	0.93
right cerebellum	24 -64 -22	5.69***	3.71**	0.94
left STG	-62 -42 8	9.72***	3.93**	1.27
left preMotor	-48 2 58	8.10***	5.35***	-0.29
left preSMA	-2 4 62	4.28**	3.80**	-0.38
right ant DLPFC	40 50 24	3.98**	3.56**	0.01
Lure-Control				
Region	**Peak**	**HC**	**PSZ**	**HC vs PSZ**
left calcarine	-18 -68 8	6.54***	4.66***	-0.29
right dACC/preSMA	6 24 44	3.71**	5.33***	-2.04*
left IPS	-40 -42 40	4.85***	4.47***	-1.24
left preMotor	-32 -4 36	3.27**	6.43***	-2.27*
right preCuneus	8 -66 44	5.32***	2.57*	1.38
right thalamus	12 -6 8	5.29***	2.55*	1.26

Supplemental Table 3. Within- and Between-Group Comparisons Outside Regions-of-Interest

Encoding-Baseline											
	Region	Area	X	Y	Z	VOX	Peak Z	HC	PSZ	HC vs PSZ
All Participants	parietal, occipital, temporal	18, 19, 7, 17, 37, 30, 40, 20, 21, 23, 36	-6	-88	-2	33597	7.82	12.65***	12.76***	1.48
	left preMotor, lat PFC	6, 9, 44, 45, 8	-46	2	32	3511	6.92	10.96***	7.49***	-1.2
	preSMA/dACC	6, 32	-2	6	60	979	6.79	7.23***	5.62***	-0.27
	right preMotor	6, 9	60	8	42	938	5.21	7.04***	5.25***	0.99
	right preMotor	6	68	-2	16	76	4.92	3.26**	3.57**	-0.5
	right ant DLPFC	10, 46	36	52	30	258	4.54	5.24***	2.68*	0.52
	right STS	22	-54	-36	4	116	4.23	3.19*	4.65***	-1.07
HC > PSZ	right IPS	7, 40	38	-52	48	189	4.27			
PSZ > HC	None									

Supplemental Table 4. Encoding - Baseline

PreCue-Baseline											
	Region	**Area**	**X**	**Y**	**Z**	**VOX**	**Peak Z**	**HC**	**PSZ**	**HC vs PSZ**
All Participants	various	6, 7, 40, 9, 32, 18, 17, 22, 8, 44	-36	-42	40	25909	7.34	10.50***	12.34***	0.55
	left ant DLPFC	10, 46	-38	54	20	909	5.46	6.89***	5.18***	-1.47
	right ant DLPFC	10, 46	46	50	22	728	5.15	5.93***	4.19**	-1.23
	right IPS	40	40	-40	46	490	4.84	5.64***	2.31*	2.44*
	brainstem		-16	-18	-40	135	4.34	5.07***	3.75**	0.83
HC > PSZ	None									
PSZ > HC	None									

Supplemental Table 5. PreCue - Baseline

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